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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

CHOI, Kyu-Pal
824-20, Yeoksam-dong, Kangnam-ku
Seoul 135-080
RÉPUBLIQUE DE CORÉE

Date of mailing (day/month/year)
01 May 2000 (01.05.00)

Applicant's or agent's file reference
PC99026-SP

IMPORTANT INFORMATION

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/KR99/00589	29 September 1999 (29.09.99)	01 October 1998 (01.10.98)

Applicant
KWANGJU INSTITUTE OF SCIENCE AND TECHNOLOGY et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SL,SZ,TZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,DE,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

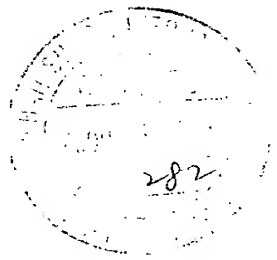
2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AE,AL,AM,AT,AZ,BA,BB,BY,CH,CR,CU,DK,DM,EE,ES,FI,GB,GD,GE,GH,GM, HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI, SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.



The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
Juan Cruz

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 May 2000 (01.05.00)	
International application No. PCT/KR99/00589	**Applicant's or agent's file reference** PC99026-SP
International filing date (day/month/year) 29 September 1999 (29.09.99)	**Priority date** (day/month/year) 01 October 1998 (01.10.98)
Applicant BYUN, Young-Ro et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

03 April 2000 (03.04.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

KR9900589

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

CHOI, Kyu-Pal
824-20, Yeoksam-dong, Kangnam-ku,
Seoul 135-080
RÉPUBLIQUE DE CORÉE

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
22 October 1999 (22.10.99)	
Applicant's or agent's file reference	**International application No.**
PC99026-SP	PCT/KR99/00589

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

KWANGJU INSTITUTE OF SCIENCE AND TECHNOLOGY et al (for all designated States except US)
BYUN, Young-Ro et al (for US)

International filing date	:	29 September 1999 (29.09.99)
Priority date(s) claimed	:	01 October 1998 (01.10.98)
Date of receipt of the record copy by the International Bureau	:	18 October 1999 (18.10.99)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,SD,SL,SZ,TZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National :AE,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,US,UZ,VN,YU,ZA,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [ ] confirmation of precautionary designations
- [X] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

R. Chrem

Telephone No. (41-22) 338.83.38

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

09/806287

PATENT COOPERATION TREATY

PCT

REC'D 01
WIPO

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
PC99026-SP		
International application No.	International filing date (*day/month/year*)	Priority Date (*day/month/year*)
PCT/KR 99/00589	29 September 1999 (29.09.1999)	1 October 1998 (01.10.1998)

RECEIVED
JUN 20 2001
TECH CENTER 1600/2900

International Patent Classification (IPC) or national classification and IPC

IPC[7]: A61K 31/203, 9/10, 9/16

Applicant

KWANGJU INSTITUTE OF SCIENCE AND TECHNOLOGY et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examination Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

- I. ☒ Basis of the opinion
- II. ☐ Priority
- III. ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV. ☐ Lack of unity of invention
- V. ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI. ☐ Certain documents cited
- VII. ☐ Certain defects in the international application
- VIII. ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
3 April 2000 (03.04.2000)	12 March 2001 (12.03.2001)
Name and mailing address of the IPEA/AT Austrian Patent Office Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/200	Authorized officer KRENN Telephone No. 1/53424/435

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/KR 99/00589

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-6,8-19 , as originally filed
pages 7 , filed with the demand
pages _____, filed with the letter of _____.

☒ the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statement) under Article 19
pages _____ , filed with the demand
pages 20-21 , filed with the letter of 27 February 2001 (27.02.2001).

☒ the drawings:
pages _____ , as originally filed
pages _____ , filed with the demand
pages 1-3 , filed with the letter of 27 February 2001 (27.02.2001).

☐ the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____.

☐ the claims, Nos. _____.

☐ the drawings, sheets/fig _____.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as „originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/KR 99/00589

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10

because:

☒ the said international application, or the said claims Nos. 10
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/KR 99/00589

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-10	YES
	Claims		NO
Inventive step (IS)	Claims	1-10	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims	10	NO

Citations and explanations (Rule 70.7)

In view of the explantations and amendments submitted with the reponse to the written opinion from 2nd March 2001 novelty and inventive step for claims 1-10 can actually be acknowledged. Since claim 10 still refers to a method of treatment of the human/animal body by therapy, industrial applicability is only given for claims 1-9.

lactic-co-glycolic acid (hereinafter referred to as "PLGA").

The biodegradable polymer is mixed with a suitable amount of a polymeric surfactant to prepare the microsphere of the invention. This polymeric surfactant is added in order to control the dissolution rate of microsphere and drug release rate.

Any of polymeric surfactants may be preferably used without limitation provided that they are amphoteric block copolymers having hydrophilic and hydrophobic groups, the example of which includes di-, tri- or multi-block copolymer or graft copolymer of the biodegradable polymer as mentioned in the above and polyethylene glycol. As such surfactant, polylactic acid-polyethyleneglycol block copolymer is preferred, with poly-L-lactic acid-polyethyleneglycol di-block copolymer (AB type di-block copolymer) (PLLA-PEG, hereinafter, referred to as "DiPLE") or poly-L-lactic acid-poly-ethyl-eneglycol-poly-L-lactic acid tri-block copolymer (PLLA-PEG-PLLA, hereinafter, referred to as "TriPLE") being most preferred.

It is obvious to those skilled in the relevant art that the mixing ratio of the above biodegradable polymer and the amphoteric polymer within the microsphere can be suitably determined according to the desired effects such as for example release pattern of retinoic acid. However, it is desirable that the ratio be selected within the range of 1:0~100 part by weight based on the biodegradable polymer.

The suitable particle size of the microsphere is within the range from 0.001 ~ 1000 ㎛, preferably from 1 to 100 ㎛.

Meanwhile, the mixing ratio of retinoic acid and microsphere is preferably

Claims

(Amended under PCT Article 34)

1. A controlled drug release system for retinoic acid characterized in that retinoic acid is incorporated into a microsphere prepared by mixing a biodegradable polymer and an amphoteric AB type di-block copolymer together, wherein the retinoic acid is selected from the group consisting of all-trans-retinoic acid, 13-cis-retinoic acid, 9-cis-retinoic acid, other retinoids and the mixture thereof.

2. The drug release system for retinoic acid according to Claim 1, wherein the biodegradable polymer is selected from the group consisting of natural polymer, synthetic polymer and the mixture thereof.

3. The drug release system for retinoic acid according to Claim 1, wherein the biodegradable polymer is selected from the group consisting of poly-L-lactic acid, poly-D,L-lactic acid, and poly(lactic-co-glycolic acid).

4. The drug release system for retinoic acid according to claim 1. wherein the amphoteric block copolymer is poly-L-lactic acid-polyethyleneglycol or poly(lactic-co-glycolic acid)-polyethyleneglycol.

5. The drug release system for retinoic acid according to Claim 1, wherein the mixing ratio of the biodegradable polymer and the amphoteric block copolymer is 1:0~100 part by weight.

6. The drug release system for retinoic acid according to Claim 1, wherein the mixing ratio of retinoic acid and microsphere is between 0.1 ~ 50 wt% based on the weight of microsphere.

7. The drug release system for retinoic acid according to Claim 1, wherein the particle size of the microsphere is between 0.001 and 1000 ㎛.

8. The drug release system for retinoic acid according to Claim 1, wherein the amphoteric block copolymer comprises 1 ~ 20 wt% of DiPLE based on the total weight of the release system.

9. The drug release system for retinoic acid according to any one of Claims 1 to 8 for use in the prevention or treatment of patients suffering from the diseases selected from the group consisting of acute promyelocytic leukemia, head and neck cancer, skin cancer, lung cancer, breast cancer, cervical cancer, bladder cancer, and acute promyelocytic leukemia.

10. A method of treating patients in need of retinoic acid administration, comprising the oral administration of the drug release system according to any one of Claims 1 to 9 into the patients.

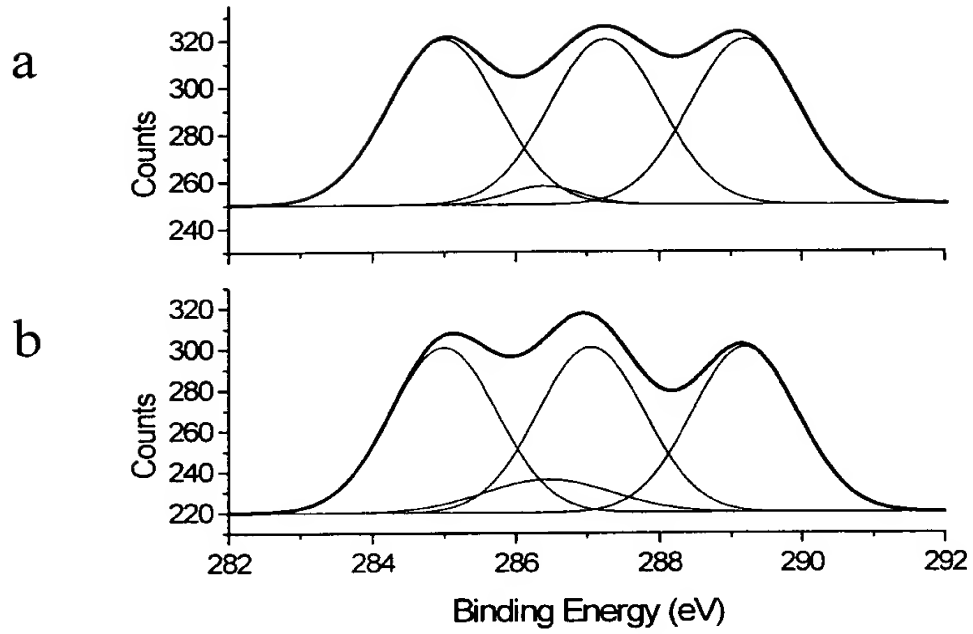

a
b
Counts
320
300
280
260
240
220
282
284
286
288
290
292
Binding Energy (eV)

Figure 1

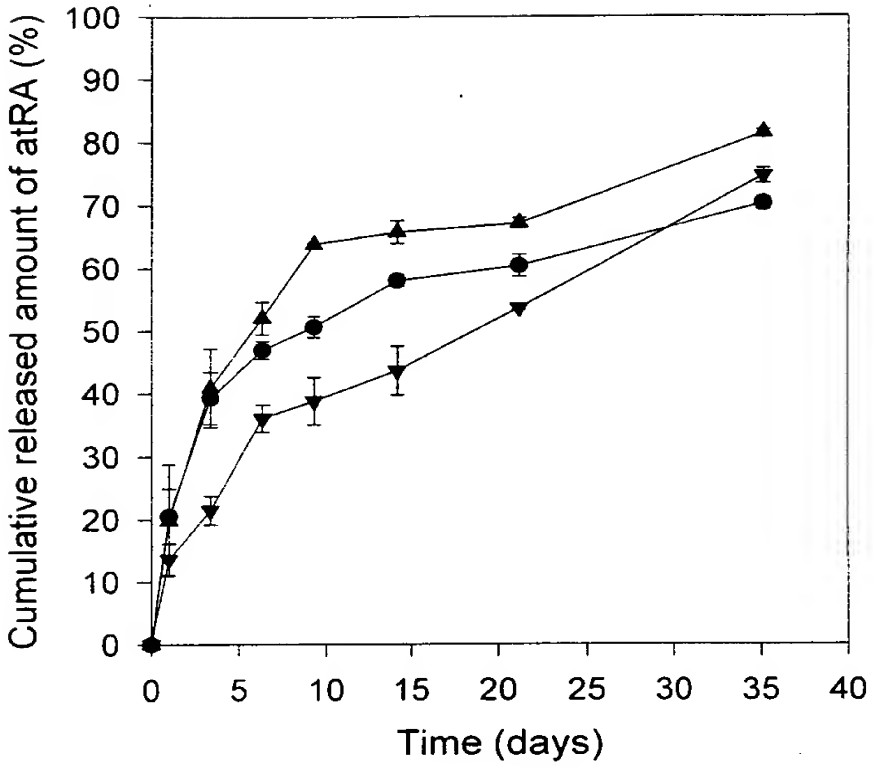

Cumulative released amount of atRA (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
Time (days)

Figure 2(a)

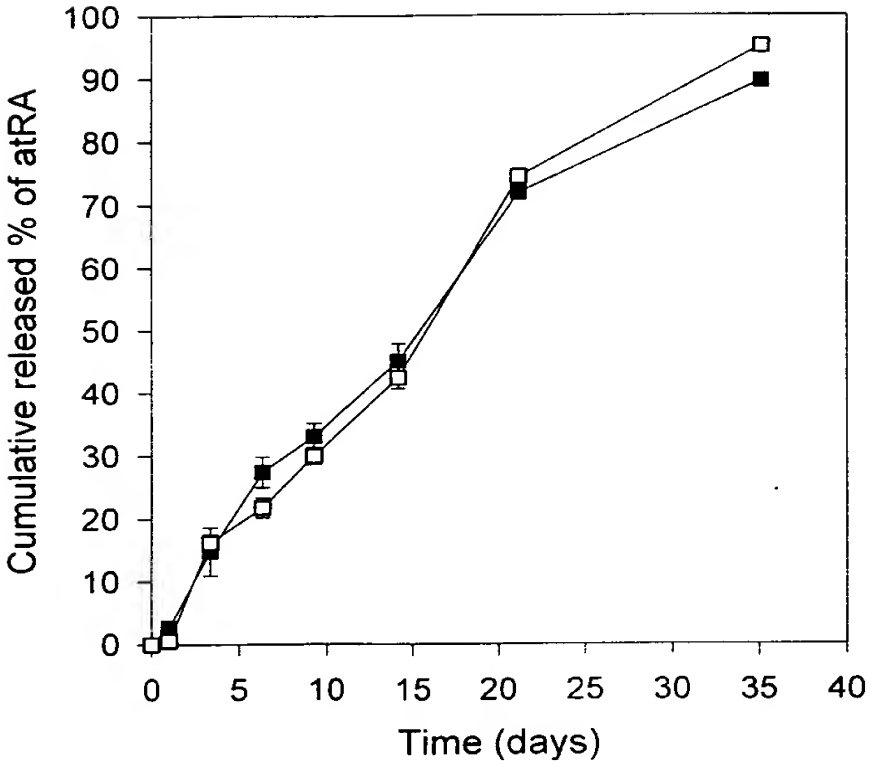

Cumulative released % of atRA
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
Time (days)

Figure 2(b)

Han Sung International Patent & Law Office

K. P. CHOI S. J. KIM
E. S. LEE S. W. RHEE
E. M. BYUN M. J. PARK
Y. G. LEE C. S. CHOI
Y. S. KIM S. J. KIM
B. K. SEO K. H. PARK
M. K. KIM J. S. CHO
E. J. KIM S. Y. LEE

4th Fl., Halla Classic Bldg.
824-11, Yeoksam-Dong,
Kangnam-Ku, Seoul, Korea

Mail : Kang Nam P.O.Box 1793
Seoul 135-080 Korea
Tel : (82-2) 555 - 6888
Fax : (82-2) 555 - 9888
(82-2) 555 - 4958
E-mail : hansung@hsip.co.kr
HomePage : www.hsip.co.kr

February 26, 2001

By Fax and DHL

Mr. Krenn
Austrian Patent Office (IPEA)
Kohlmarkt 8-10,
A-1014 Vienna
Austria

Re: International Appln. No. PCT/KR99/00589
Filed on September 29, 1999
Priority Date : October 1, 1998
Applicant: Kwangju Institute of Science and Technology et al.
Our ref.: PC99026-SP

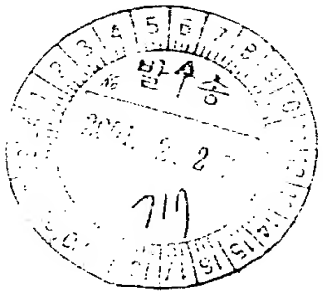
Dear Mr. Krenn:

This is in response to the Written Opinion dated January 30, 2001 regarding the above-identified application.

In order to distinguish the present invention from the cited references, please replace the claims of the present application by the amended claims enclosed with this letter. As shown in the enclosed claims, the retinoic acid has been restricted to"all-trans-retinoic aicd, 13-cis-retinoic acid, 9-cis-retinoic aicd, other retinoids and the mixture thereof".

The present invention prepares a microsphere by mixing a biodegradable polymer such as PLLA, PDLA or PLGA and an amphoteric AB type di-block copolymer such as PLA-PEG or PLGA-PEG together, but the references prepares a microsphere by using only a biodegradable polymer or PLA-PEG block copolymer. The references never teach or suggest a combination of the above two types of polymers for the preparation of the microsphere. Further, the references have no concrete disclosure regarding the use of "all-tran-retinoic aicd, 13-cis-retinoic acid, 9-cis-retinoic aicd, other retinoids and the mixture thereof" as the retinoic acid.

The microsphere in which the above two types of polymers are mixed together as in the present invention has the following superior effects and advantages when compared with the microsphere using only one of the the above polymers:



First, since the PLA-PEG block copolymer mixed with the biodegradable polymer is amphoteric, it is well dispersed in the interior and surface of the microsphere.by making the microsphere surface to be hydrophilic. Therefore, when the microsphere is dispersed in the buffer, dispersion is evenly made without addition of any surfactant. However, a conventional biodegradable microsphere which does not use the above block copolymer has hydrophobic surface, in order to administer it to the body it must be dispersed in an aqueous solution with addition of surfactant.

Specifically, a conventional PLLA microsphere, which do not contain PLE, is not dispersed in PBS, but could be dispersed only in the presence of surfactant. In contrast, PLLA/PLE microspheres are well dispersed in PBS without addition of any surfactants. It was also found that as the PLE content was increased, the dispersion of the microspheres in PBS improved. The XPS analysis confirmed that this good dispersity is due to the PEG block of PLE on the microsphere surfaces, as shown on the attached Fig. 1. (Note that Fig. 1 shows C_{1s} XPS spectra of (a) the microspheres containing 4 wt% PLE and (b) the microspheres containing 8wt% PLE). The characteristic peak of the PEG block was observed at 286.4 eV of the C_{1s} signal. Peaks at 285.0, 287.05 and 289.2 eV were assigned to the binding energy of -CH-, -CO-, and $-CO_2$ - in PLLA, respectively. The ratio of areas between the peaks C-C-O (PEG block of PLE) and CH (PLLA block of PLE and matrix PLLA) was calculated from the XPS data. Their values were 8% for PLE 4 microspheres and 23% for PLE8 microspheres. These values were higher than those of the theretical values, which were 2% for PLE4 microspheres and 3.8% for PLE8 microspheres. The XPS method analyzes the composition within a thickness of 100 Å from the microsphere suface. It can be therefore said from the XPS data that the content of PLE is higher near the microsphere surface (in the range of 100 Å from the surface) than in the region beyond 100 Å from the microsphere surface.

Second, the microsphere in which the biodegradable polymer and the block copolymer are mixed together can be sterilized by ethylene oxide gas. The contained block copolymer increases the crystallinity of biodegradable polymer of the microsphere, thereby the shape of microsphere does not change even after sterilization of ethylene oxide gas. However, for a conventional microsphere prepared from a single biodegradable polymer, when it is sterilized by ethylene oxide gas, the microspheres are aggregated each other, therefore the sterilization by ethylene oxide gas is not possible and sterilization by γ-ray is possible. However, the sterilization by γ-ray reduces the molecular weight of the biodegrabale polymer and optionally a chemical reaction between drug contained in the microsphere and microsphere can be occurred. Therefore, the advantages that the microsphere can be sterilized by ethylene oxide gas according to the present invention are very important in extending the scope of their application so that it can be administered to various drugs.

Third, the block copolymer mixed with the biodegradable polymer can control the release pattern of drug according to the content. Especially, for the retinoic acid suggested in the present invention, the change of release pattern according to the function of the block copolymer showed significant.

The reason is that while the microsphere is hydrated by hydrophilic PEG of the block polymer, acid-catalytic hydrolysis of biodegradable polymer is accelerated.

The release pattern of atRA from the microsphere was dependent upon the content of PLE and atRA. See Fig. 2 wherein (a) 2wt% atRA, (●)PLE0/RA2, (▲)PLE4/RA2, (▼)PLE8/RA2; (╥) 8wt% atRA, (■)PLE4/RA8, (□)PLE8/RA8. The PLE0/RA2 microspheres, which contained 2wt% of atRA without PLE, showed a pseudo first-order release profile of atRA; that is, a burst effect at the early stage was followed by a slow release of atRA. In contrast, the PLE8/RA8 micropheses, containing 8wt% atRA and 8 wt%PLE, presented a nearly constant release rate of atRA (i.e. pseudo zero-order release profile) for 5 weeks. The cumulative released amount of atRA for 5 weeks was about 95%. As the content of PLE and atRA were increased, the release pattern of atRA shifted from a first-order to a pseudo zero-order. The release pattern of such first-order profile is to maintain retinoic acid in a constant release rate for a long time and plays an important role in constantly maintaining the blood concentration of retinoic aicd.

Therefore, it is apparent that the above superior and unexpected properties and advantages constitute a novel and surprising result and, thus, the amended claims 1-10 in the present application shows inventive step over the prior art references.

With the above explanation and proposed amendment, it is believed that the Applicant has met the requirements set forth in the Written Opinion. It is therefore requested that a positive International Preliminary Examination Report be issued.

Respectfully Submitted,
HAN SUNG International
Patent & Law Office

By: Kyu Pal Choi
Kyu Pal Choi, Patent Attorney

Encls. 1. Figures 1 and 2
2. Proposed Claims

Claims

(Amended under PCT Article 34)

1. A controlled drug release system for retinoic acid characterized in that retinoic acid is incorporated into a microsphere prepared by mixing a biodegradable polymer and an amphoteric AB type di-block copolymer together, wherein the retinoic acid is selected from the group consisting of all-trans-retinoic acid, 13-cis-retinoic acid, 9-cis-retinoic acid, other retinoids and the mixture thereof.

2. The drug release system for retinoic acid according to Claim 1, wherein the biodegradable polymer is selected from the group consisting of natural polymer, synthetic polymer and the mixture thereof.

3. The drug release system for retinoic acid according to Claim 1, wherein the biodegradable polymer is selected from the group consisting of poly-L-lactic acid, poly-D,L-lactic acid, and poly(lactic-co-glycolic acid).

4. The drug release system for retinoic acid according to claim 1. wherein the amphoteric block copolymer is poly-L-lactic acid-polyethyleneglycol or poly(lactic-co-glycolic acid)-polyethyleneglycol.

5. The drug release system for retinoic acid according to Claim 1, wherein the mixing ratio of the biodegradable polymer and the amphoteric block copolymer is 1:0~100 part by weight.

6. The drug release system for retinoic acid according to Claim 1, wherein the mixing ratio of retinoic acid and microsphere is between 0.1 ~ 50 wt% based on the weight of microsphere.

7. The drug release system for retinoic acid according to Claim 1, wherein the particle size of the microsphere is between 0.001 and 1000 ㎛.

8. The drug release system for retinoic acid according to Claim 1, wherein the amphoteric block copolymer comprises 1 ~ 20 wt% of DiPLE based on the total weight of the release system.

9. The drug release system for retinoic acid according to any one of Claims 1 to 8 for use in the prevention or treatment of patients suffering from the diseases selected from the group consisting of acute promyelocytic leukemia, head and neck cancer, skin cancer, lung cancer, breast cancer, cervical cancer, bladder cancer, and acute promyelocytic leukemia.

10. A method of treating patients in need of retinoic acid administration, comprising the oral administration of the drug release system according to any one of Claims 1 to 9 into the patients.

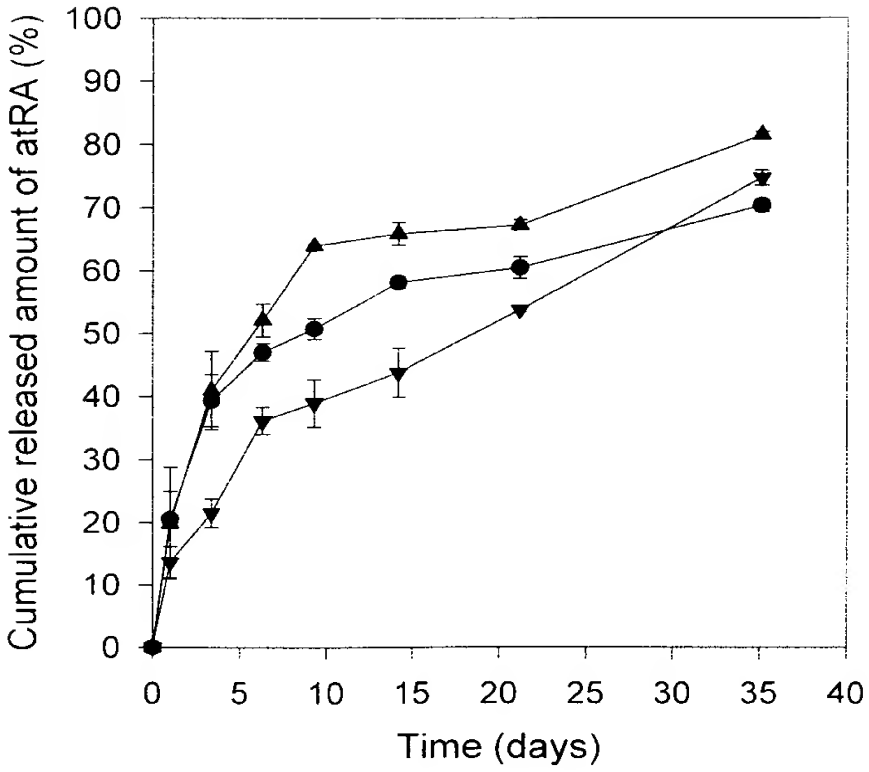

Cumulative released amount of atRA (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
Time (days)

Figure 2(a)

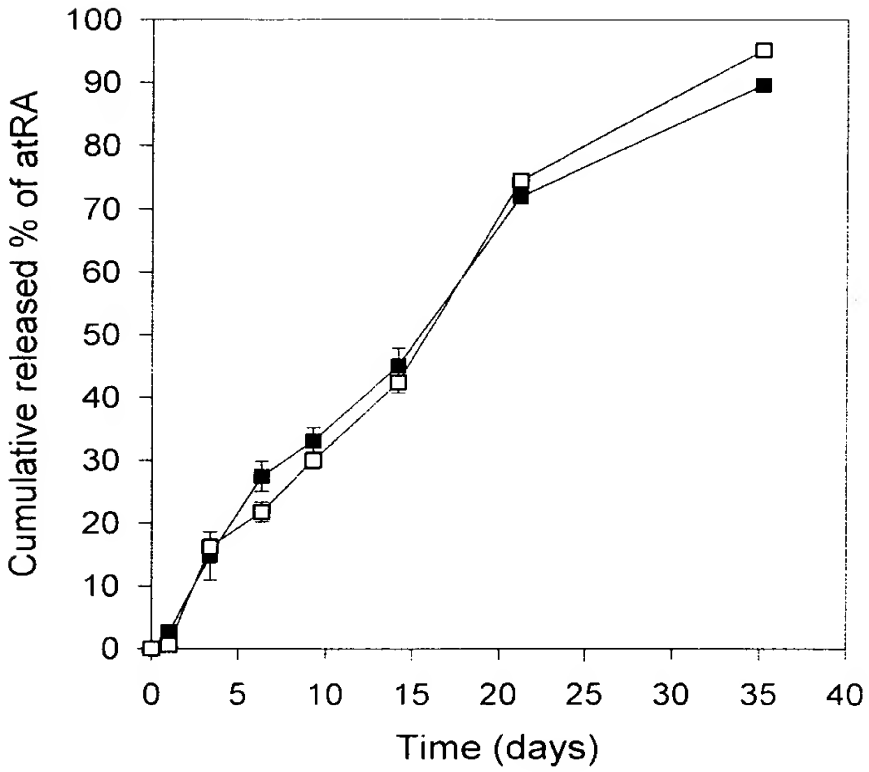

Cumulative released % of atRA
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
Time (days)

Figure 2(b)

ATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

CHOI, Kyu Pal
824-20, Yeoksam-dong,
Kangnam-ku,
Seoul 135-080,
Republic of Korea

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)* 30 January 2001 (30.01.01)	
Applicant's or agent's file reference PC99026-SP	**REPLY DUE** within 1 months/~~days~~ from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/KR 99/00589	29 September 1999 (29.09.99)	01 October 1998 (01.10.98)

International Patent Classification (IPC) or both national classification and IPC
IPC[6]: A 61 K 31/203, 9/10, 9/16

Applicant
KWANGJU INSTITUTE OF SCIENCE AND TECHNOLOGY et al.

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:
   - I. ☒ Basis of the opinion
   - II. ☐ Priority
   - III. ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV. ☐ Lack of unity of invention
   - V. ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI. ☐ Certain documents cited
   - VII. ☐ Certain defects in the international application
   - VIII. ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

   Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis. For an informal communication with the examiner, see Rule 66.6.

   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 01 February 2001 (01.02.01).

Name and mailing address of the IPEA/AT	Authorized officer
Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna	Krenn
Facsimile No. 1/53424/200	Telephone No. 1/53424/435

Form PCT/IPEA/408 (cover sheet) (July 1998)

ernational application No.

ITEN OPINION

PCT/KR 99/00589

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-6, 8-19, as originally filed
pages 7, filed with the demand
pages _____, filed with the letter of _____.

☒ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under Article 19
pages 20, 21, filed with the demand
pages _____, filed with the letter of _____.

☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____.

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____.

☐ the claims, Nos. _____.

☐ the drawings, sheets/fig _____.

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*

WR[redacted]EN OPINION

[redacted]plication/Reference No.
PCT/KR99/00589

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrial applicable have not been examined in respect of:

☐ the entire international application

☒ claim No. 10 (see remark)

Because:

☒ the said international application, or the said claim No.10 relates to the following subject matter

which does not require an international preliminary examination (*specify*):

Remark:

According to PCT-Article 17, rule 39.1.iv therapeutic methods of treatment of the human/animal body are excluded from patentability; thus claim 10 referring to such a method is considered to be a non-patentable invention.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos.

are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no

meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

WRITTEN OPINION

Application/Reference No.
PCT/KR99/00589

V. Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2,9,10	YES
	Claims	1,3-8	NO
Inventive Step (IS)	Claims	9,10	YES
	Claims	1-8	NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims	10	NO

2. Citations and explanations:

Claim 1 of WO 9715287 A1 refers to an active agent suspended in a biodegradable block copolymer comprising a hydrophobic A polymer block composed of at least two α-hydroxy acid units and a hydrophilic B polymer block composed of a polyethylene glycol. Even though the disclosure made in WO 9715287 A1 is preferably directed to compounds showing a higher polymerization order, di-block copolymers are not explicitly excluded from the scope of invention. Since the document also mentions the use of such drug release systems for the administration of anticancer agents - retinoids are known as anti-neoplastic agents - the subject matter of at least claims 1 and 3-8 of the present application appears to be neither new nor inventive.

The disclosure made in WO 9628143 A1 focuses on microparticles composed of a drug and a polymeric matrix defined as a ABA-tri-block copolymer. Since the scope of invention of the present application has actually been limited to di-block copolymers, the documents is no more of any relevance of the examination of the present application.

US 5534261 A as well as the article published by GIORDANO et al. promote the delivery of retinoids by release systems such as microspheres, biodegradable polymer films, liposomes, etc..

For all the limitations made with the letter of 3 April 2000 both novelty and inventive step are still lacking. Claims 9 and 10 referring to a specific application of such formulation is considered to be new as well as inventive.

According to PCT-Article 17, rule 39.1.iv patentability is not given for claims concerning methods of therapeutic treatment of the human or animal body; thus claim 10 referring to such a therapeutic method is not industrial applicable.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

AUSTRIAN PATENT OFFICE Identification of IPEA	03 April 2000 (03.04.00) Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: PC99026-SP

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/KR 99/00589	29 September 1999 (29.09.1999)	01 October 1998 (01.10.1998)

Title of invention
CONTROLLED DRUG RELEASE SYSTEM OF RETINOIC ACID

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KWANGJU INSTITUTE OF SCIENCE AND TECHNOLOGY
572, Ssangam-dong, Kwangsan-ku,
506-712 Kwangju, Republic of Korea

Telephone No.: (82-62) 970-2302
Facsimile No.: (82-62) 970-2304
Teleprinter No.:

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
KR	KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SHIN POONG PHARMACEUTICAL CO., LTD.
434-4, Moknae-dong, Ansan-shi,
425-100 Kyunggi-do, Republic of Korea

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
KR	KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BYUN, Young-Ro
Keumkwang Apt. 103-1305, Wallgae-dong,
Kwangsan-ku, 506-302 Kwangju, Republic of Korea

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
KR	KR

[X] Further applicants are indicated on a continuation sheet.

Sheet No. 2

International application No. PCT/KR 99/00589

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet is not to be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KIM, Sang-Yoon
Woosung Apt. 3-707, Daechi 3-dong,
Kangnam-ku, 135-283 Seoul, Republic of Korea

State *(i.e. country)* of nationality: KR	State *(i.e. country)* of residence: KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KIM, Sun-Hee
Woosung Apt. 3-707, Daechi 3-dong,
Kangnam-ku, 135-283 Seoul, Republic of Korea

State *(i.e. country)* of nationality: KR	State *(i.e. country)* of residence: KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CHOI, Yong-Doo
Jeungheung Park 2-1508, Nongsung 1-dong,
Seo-ku, 502-201 Kwangju, Republic of Korea

State *(i.e. country)* of nationality: KR	State *(i.e. country)* of residence: KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HAN, In-Suk
G 105-1025, East Olympic Lease Core,
Salt Lake-city, UT 84117, United States of America

State *(i.e. country)* of nationality: KR	State *(i.e. country)* of residence: US

[X] Further applicants are indicated on another continuation sheet.

Sheet No. 3.

International application No.
PCT/KR 99/00589

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet is not to be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LEE, Kwang-Sun
Kwangjang Apt. 3-605, Yoido-dong,
Yongdungpo-ku, 150-010 Seoul,
Republic of Korea

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
KR	KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KIM, Chul-Hee
Chungku Apt. 210-1050, Yangjimaeul,
Soonae-dong, Bundang-ku,
463-020 Sungnam-shi,
Republic of Korea

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
KR	KR

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/KR 99/00589

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CHOI, Kyu-Pal
824-20, Yeoksam-dong, Kangnam-ku,
135-080 Seoul, Republic of Korea

Telephone No.: (82-2) 555-6888

Facsimile No.: (82-2) 555-9888

Teleprinter No.:

[ ] Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the International Preliminary Examining Authority*

(i) [X] to start the international preliminary examination on the basis of the international application as originally filed.

(ii) [X] to take into account the amendments under Article 34 of

- [X] the description (amendments attached).
- [X] the claims (amendments attached).
- [ ] the drawings (amendments attached).

(iii) [ ] to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).

(iv) [ ] to disregard any amendments of the claims made under Article 19 and to consider them as reversed.

(v) [ ] to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Box No. V ELECTION OF STATES

[☒] The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)* except .....

(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

Sheet No. 5.

International application No.
PCT/KR 99/00589

Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. amendments under Article 34				
description	: 1	sheets	[X]	[ ]
claims	: 2	sheets	[X]	[ ]
drawings	:	sheets	[ ]	[ ]
2. letter accompanying amendments under Article 34	:	sheets	[ ]	[ ]
3. copy of amendments under Article 19	:	sheets	[ ]	[ ]
4. copy of statement under Article 19	:	sheets	[ ]	[ ]
5. other *(specify)*:	:	sheets	[ ]	[ ]

The demand is also accompanied by the item(s) marked below:

1. [ ] separate signed power of attorney
2. [ ] copy of general power of attorney
3. [ ] statement explaining lack of signature
4. [X] fee calculation sheet
5. [X] other *(specify)*: remittance receipt

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

CHOI, Kyu-Pal

Kyu Pal Choi

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND: 03 April 2000 (03.04.00)

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. [ ] The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. [ ] The applicant has been informed accordingly.

4. [ ] The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. [ ] Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/KR 99/00589	For International Preliminary Examining Authority use only
Applicant's or agent's file reference PC99026-SP	Date stamp of the IPEA

Applicant
KWANGJU INSTITUTE OF SCIENCE AND TECHNOLOGY et al.

Calculation of prescribed fees

1. Preliminary examination fee	2,200 ATS	P
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	2,036.52 ATS	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	4,236.52 ATS	TOTAL

Mode of Payment

☐	authorization to charge deposit account with the IPEA (see below)	☒	cash
☐	cheque	☐	revenue stamps
☐	postal money order	☐	coupons
☐	bank draft	☐	other *(specify)*:

ATS 4,236
2000. 3. 29

Deposit Account Authorization *(this mode of payment may not be available at all IPEAs)*

The IPEA/ _____ ☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☐ *(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

Deposit Account Number _____ Date *(day/month/year)* _____ Signature _____

See Notes to the fee calculation sheet

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

CHOI, Kyu-Pal
824-20, Yeoksam-dong, Kangnam-ku,
Seoul 135-080
RÉPUBLIQUE DE CORÉE

Date of mailing (day/month/year) 27 October 1999 (27.10.99)	
Applicant's or agent's file reference PC99026-SP	**IMPORTANT NOTIFICATION**
International application No. PCT/KR99/00589	International filing date (day/month/year) 29 September 1999 (29.09.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 01 October 1998 (01.10.98)
Applicant KWANGJU INSTITUTE OF SCIENCE AND TECHNOLOGY et al	

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2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

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Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
01 Octo 1998 (01.10.98)	1998/41426	KR	26 Octo 1999 (26.10.99)

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The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Taïeb Akremi
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P TENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

To:
CHOI, Kyu-Pal
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NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 13 April 2000 (13.04.00)	
Applicant's or agent's file reference PC99026-SP	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/KR99/00589	29 September 1999 (29.09.99)	01 October 1998 (01.10.98)

Applicant
KWANGJU INSTITUTE OF SCIENCE AND TECHNOLOGY et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   13 April 2000 (13.04.00) under No. WO 00/19996

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

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If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

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NOTICE [redacted]RMING THE APPLICANT OF THE CO[redacted]UNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
13 April 2000 (13.04.00)	
Applicant's or agent's file reference	**International application No.**
PC99026-SP	PCT/KR99/00589

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PC99026-SP		
International application No.	International filing date (*day/month/year*)	(Earliest) Priority Date (*day/month/year*)
PCT/KR 99/00589	29 September 1999 (29.09.99)	01 October 1998 (01.10.98)
Applicant		
KWANGJU INSTITUTE OF SCIENCE AND TECHNOLOGY et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.: 1a - 1d

☒ as suggested by the applicant. ☐ None of the figures.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

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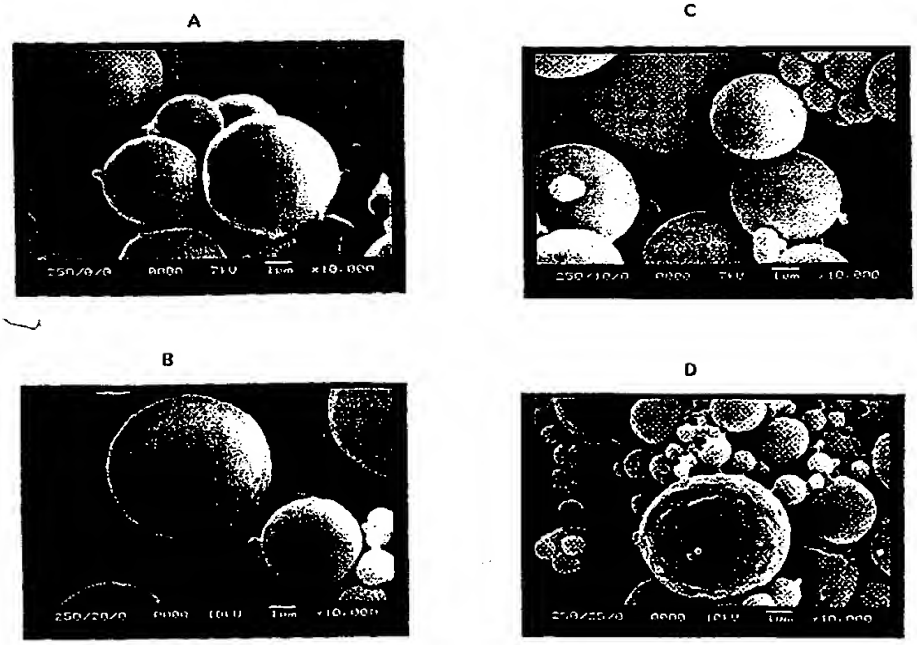
(54) Title: CONTROLLED DRUG RELEASE SYSTEM OF RETINOIC ACID



(57) Abstract

The present invention relates to a controlled drug release system in which a certain ratio of retinoic acid is incorporated into a microsphere comprising biodegradable polymer and amphoteric block copolymer having both hydrophilic and hydrophobic groups.

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CONTROLLED DRUG RELEASE SYSTEM OF RETINOIC ACID

Technical Field

The present invention relates to a controlled drug release system in which a certain ratio of retinoic acid(hereinafter referred to as "RA") is incorporated into a microsphere comprising biodegradable polymer and amphoteric copolymer having both hydrophilic and hydrophobic groups.

Background Art

Retinoic acid has been known to have roles in controlling the differentiation and growth of cells and reportedly inhibits carcinogenesis in various epithelial tissues. It has especially been known to have good effects on the prevention and treatment of cancers such as head and neck cancer, skin cancer, lung cancer, breast cancer, cervical cancer, bladder cancer, etc. and also exhibits efficacy in patients suffering from acute promyelocytic leukemia [See, Blood 76, 1704-1709 (1990), Blood 78, 1413-1419 (1991); and, The New England Journal of Medicine 324, 1385-1393 (1991)].

However, upon continuous repetitive administration of retinoic acid, drug level in blood is rapidly decreased compared with the early stage of treatment [Blood 79, 299-303 (1992)], and the diseases are recurred within a short period [Cancer Research 52, 2138-2142 (1992)]. This is because the oral administration of retinoic acid induces cytochrome P450 enzyme which metabolizes retinoic acid. Even in a case where a small amount of retinoic acid is administered, cytochrome P450 is induced, and repeated administration would accelerate the metabolism by the enzyme and thus it

is impossible to maintain effective retinoic acid level in blood. If the level of retinoic acid increases, severe side toxic effects would appear, and even result in difficulty in breathing, spasm, comatose state which leads to death. In order to solve these problems, drug release systems for retinoic acid using liposome [Leukemia Research 18, 587-596 (1994)] or nanoparticle [International Journal of Pharmaceutics 131, 191-200 (1996)] have been tried, but these systems have a drawback that the control of drug release is difficult.

As another prior art reference for delayed retinoic acid release system, it has been reported that retinoic acid was released over 40 days by incorporating retinoic acid into a microsphere prepared from lactic acid and poly(lactic-co-glycolic acid, hereinafter referred to as "PLGA") [See, Investigative Ophthalmology & Visual Science 34, 2743-2751 (1993)]. The system was focused on the treatment of proliferative vitreoretinopathy. However, the microsphere prepared by this technique has a drawback that it is difficult to be dispersed into an aqueous phase. In addition, since ethylene oxide is impossible for applying gas sterilization, gamma-ray sterilization should be used. Even if, such gamma-ray sterilization is carried out on the microsphere, the molecular weight thereof is decreased. Further, this prior art system fails to teach the use of amphoteric copolymer in controlling the dissolution rate of the microsphere and the release of retinoic acid.

Disclosure of Invention

It is therefore an object of the present invention to solve the problems associated with the prior art release system.

Another object of the present invention is to provide a controlled drug release system for retinoic acid which comprises microsphere in which biodegradable polymer and amphoteric block copolymer and retinoic acid incorporated into the microsphere.

Further objects and advantages of the invention will become apparent through reading the remainder of the specification.

The foregoing has outlined some of the more pertinent objects of the present invention. These objects should be construed to be merely illustrative of some of the more pertinent features of the invention. Many other beneficial results can be obtained by applying the disclosed invention in a different manner or by modifying the invention within the scope of the disclosure. Accordingly, other objects and a more thorough understanding of the invention may be found by referring to the detailed description of the preferred embodiment in addition to the scope of the invention defined by the claims.

Brief Description Of Drawings

Fig. 1 is a photograph showing the morphology of microsphere according to the contents of poly-L-lactic acid-polyethyleneglycol block copolymer: (a)-without DiPLE; (b)-with 4% of DiPLE; (c)-with 8wt% of DiPLE; and (d)-with 10wt% of DiPLE.

Fig. 2 represents a graph in which the surface compositions of the microspheres were analysed with X-ray photoelectric spectrum: (a)-microsphere containing 8% of DiPLE; (b)-microsphere containing 4% of DiPLE; and (c)-surface composition of DiPLE test sample.

Fig. 3 is a photograph showing the morphology of poly-D,L-lactic acid microsphere according to the mixing ratio of TriPLE: (a) - 5 wt% of TriPLE 2-1; (b) - 15 wt% of TriPLE 2-1; (c) - 100 wt% of TriPLE 2-1; (d) - 5wt% of TriPLE 3-1; (e) - 20Wt% of TriPLE 3-1; and (f) - 100 wt% of TriPLE 3-1.

Fig. 4 is a photograph showing the morphology of poly-L-lactic acid microsphere according to the content of retinoic acid (RA);
(a) microsphere size: 1~10 μm, RA content: 4 wt%;
(b) microsphere size: 1~10 μm, RA content: 8 wt%;
(c) microsphere size 20~100 μm, RA content: 4 wt%;
(d) TriPLE 2-1 microsphere size 20~100 μm, RA content: 5 wt%; and
(e) TriPLE 2-1 microsphere size 20~100 μm, RA content: 10 wt%.

Fig. 5 is a graph showing drug release curves according to DiPLE and RA content within the microsphere, in which (a) represents the curve when RA is 2 wt%, and DiPLE varies at 0 wt%, 4 wt%, and 8 wt%;
(b) represents the curve when RA is 4 wt%, and DiPLE varies at 0 wt%, 4 wt%, 8 wt%; and
(c) represents the curve when RA is 8 wt%, and DiPLE varies at 4 wt%, 8 wt%.

Fig. 6 is a photograph showing inhibition of tumour growth by the drug release system according to the invention, in which
(a) represents the control tumour-induced mouse at five weeks after administering a release system which does not contain retinoic acid; and
(b) represents the test mouse at five weeks after administering the release system according to the invention which contains retinoic acid(DiPLE 8

wt%, RA 4 wt%).

Best Mode For Carrying Out The Invention

Hereinafter, the invention will be illustrated in more detail.

The present inventors have conducted an extensive research for many years in order to develop a new drug release system in which the prior art drawbacks are eliminated. As a result, the inventors have surprisingly discovered that when retinoic acid is incorporated into a microsphere prepared from biodegradable polymer such as PLLA, PDLLA, or PLGA and amphoteric poly-L-lactic acid-polyethyleneglycol block copolymer("PLE"), retinoic acid is released over long term period in a sustained pattern and thus, this release system can improve the prior art drawbacks, for example can reduce resistance induction by the conventional retinoic acid administration, and can be used in the prevention or treatment of leukemia and various cancers, and have completed the present invention.

In one aspect, the present invention provides a controlled drug release system which comprises a microsphere in which biodegradable polymer and amphoteric block copolymer are mixed together and retinoic acid incorporated into the microsphere.

Retinoic acid which can be used as the active ingredient in the drug release system according to the present invention has no limitation and include, for example, all-trans-retinoic acid, 13-cis-retinoic acid, 9-cis-retinoic acid, other retinoids and the mixture thereof.

As for the biodegradable polymer used in the preparation of microsphere,

any polymeric material can be used without any limitation if it has bioavailable and biodegradable properties as the support for the microsphere. Such polymers include natural and synthetic origins, and the examples thereof are set forth in Table 1 below.

Table 1. Biodegradable polymer

Polymer	Classification	Specific polymer
Synthetic polymer	Polyesters	Poly(L-lactic acid), Poly(D,L-lactic acid) Poly(glycolic acid), Poly(lactic-co-glycolic acid), Polyhydroxybutyrate, poly(valerolactone), Poly(ε -caprolactone)
	Polyanhydrides	Poly[bis(p-carboxyphenoxy)propane-cosebacic acid], Poly(fatty acid dimer-co-sebacic acid)
	Polyphosphazenes	Aryloxyphosphazene polymer, Amino acid ester system
	Poly(ortho esters)	
Natural polymer	Polysaccharides	Cellulose, Starch, Chondroitin sulfate
	Proteins	Albumin, Collagen

The above polymer can be used either solely or in admixture of two or more individual polymers.

The biodegradable polymer which can be desirably used in the present invention includes poly-L-lactic acid(hereinafter referred to "PLLA"), Poly-D,L-lactic acid (hereinafter referred to as "PDLLA"), and poly

lactic-co-glycolic acid (hereinafter referred to as "PLGA").

The biodegradable polymer is mixed with a suitable amount of a polymeric surfactant to prepare the microsphere of the invention. This polymeric surfactant is added in order to control the dissolution rate of microsphere and drug release rate.

Any of polymeric surfactants may be preferably used without limitation provided that they are amphoteric block copolymers having hydrophilic and hydrophobic groups, the example of which includes di-, tri- or multi-block copolymer or graft copolymer of the biodegradable polymer as mentioned in the above and polyethylene glycol. As such surfactant, polylactic acid-polyethyleneglycol block copolymer is preferred, with poly-L-lactic acid-polyethyleneglycol di-block copolymer (PLLA-PEG, hereinafter, referred to as "DiPLE") or poly-L-lactic acid-polyethyleneglycol-poly-L-lactic acid tri-block copolymer (PLLA-PEG-PLLA, hereinafter, referred to as "TriPLE") being most preferred.

It is obvious to those skilled in the relevant art that the mixing ratio of the above biodegradable polymer and the amphoteric polymer within the microsphere can be suitably determined according to the desired effects such as for example release pattern of retinoic acid. However, it is desirable that the ratio be selected within the range of 1:0~100 part by weight based on the biodegradable polymer.

The suitable particle size of the microsphere is within the range from 0.001 ~ 1000 ㎛, preferably from 1 to 100 ㎛.

Meanwhile, the mixing ratio of retinoic acid and microsphere is preferably

within the range between 0.1 ~ 50 wt% based on the weight of microsphere.

Examples

The present invention will be described in greater detail through the following examples. The examples are presented for illustrating purposes only and should not be construed as limiting the invention which is properly delineated in the claims.

Example 1. Synthesis of polymeric surfactant

1.1. Synthesis of poly-L-lactic acid-polyethyleneglycol di-block copolymer

Poly-L-lactic acid-polyethylene glycol di-block copolymer used as the polymeric surfactant (DiPLE) was synthesized by ring opening polymerization of L-lactide using mono-methoxy polyethyleneglycol as the initiator. L-lactide was recrystalized twice from ethyl acetate and monomethoxy polyethyleneglycol was used after drying under reduced pressure at 60℃ for 8 hours.

First, 6.507g of L-lactide, 2g of monomethoxy polyethyleneglycol(Mn 5,000), and 45㎖ of toluene were poured into a three-necked flask equipped with stirrer, nitrogen inlet and reflux condenser and heated at 70 ℃ until two reactants are completely dissolved into toluene. Continuously, 65mg of catalyst, stannous octoate was added into the flask and the solvent, toluene was refluxed at 110℃ for 24 hours. After removing the solvent under reduced pressure, the resulting product was dissolved into chloroform, and then purified by precipitating into each of mixed solutions

of acetone/diethyl ether(1:4 v/v) and methanol/hexanol(4:1 v/v) to give the poly-L-lactic acid-polyethylene glycol di-block copolymer.

1.2: Synthesis of poly-L-lactic acid-polyethylene glycol tri-block copolymer

Poly-L-lactic acid-polyethylene glycol-poly-L-lactic acid (PLLA-PEG-PLLA) tri-block copolymer used as the polymeric surfactant(TriPLE) was synthesized by ring opening polymerization of L-lactide using polyethyleneglycol as the initiator. The initiator, polyethyleneglycol (trademarks designated molecular weight 4600, 2000, 600, Aldrich chemical company, USA) was used after dissolving into chloroform, precipitating into diethyl ether and then drying at vacuum.

The synthesis was carried out in the same manner as in the di-block copolymer (DiPLE) synthesis and the amounts added upon synthesis are shown in Table 2 below.

Table 2. The amounts of polyethyleneglycol, L-lactide, and stannous octoate

Block copolymer	PEG M_n by GPC	PEG (g)	L-lactide (g)	St-oct (mg)
TriPLE 1-1	5,200	2.00	7.84	78
TriPLE 1-2		2.00	12.20	12
TriPLE 1-3		1.00	8.25	82
TriPLE 2-1	2,200	1.00	9.00	90
TriPLE 2-2		0.60	9.38	94
TriPLE 2-3		0.50	9.50	95
TriPLE 3-1	616	0.30	9.00	90
TriPLE 3-2		0.203	9.314	93
TriPLE 3-3		0.153	9.504	95

The result of analysis on the final product of poly-L-lactic acid-polyethylene glycol block copolymer is as follows:

^{1}H-NMR (400 MHz, chloroform($CDCl_3$)): δ 1.58 (-CH_3 of PLLA), 5.19 (-CH of PLLA), 3.65 (-O-CH_2-CH_2 of PEG)

FT-IR: 1758cm^{-1} (CO), 1300-1000cm^{-1} (COO), 2882 cm^{-1} (CH_2)

In addition, the molecular weight and thermal characterization of the synthesized polymer measured by gas permeation chromatograph, etc. were represented in Table 3.

Table 3. The molecular weight and thermal characterization of the synthesized polymer

Block copolymer	Chemical structure	M_n [1]	MWD [1]	T_g(℃) [2]	T_m (℃) [2]
DiPLE	EG_{113}-LA_{191}	32,500	1.46	18~40	169
TriPLE 1-1	LA_{145}-EG_{118}-LA_{145}	26,000	1.23	51.2	167
TriPLE 1-2	LA_{223}-EG_{118}-LA_{223}	38,700	1.21	51.8	173.5
TriPLE 1-3	LA_{275}-EG_{118}-LA_{275}	44,800	1.19	52.6	175.4
TriPLE 2-1	LA_{142}-EG_{50}-LA_{142}	22,600	1.48	55.1	175.1
TriPLE 2-2	LA_{217}-EG_{50}-LA_{217}	33,500	1.30	55.8	178.1
TriPLE 2-3	LA_{312}-EG_{50}-LA_{312}	47,100	1.31	56.3	175.4
TriPLE 3-1	LA_{140}-EG_{14}-LA_{140}	20,800	1.23	50.2	169.5
TriPLE 3-2	LA_{233}-EG_{14}-LA_{233}	34,200	1.22	52.7	172.9
TriPLE 3-3	LA_{340}-EG_{14}-LA_{340}	49,500	1.21	53.9	173.1

[1] : determined by GPC (gel permeation chromatography)

[2] : determined by DSC (differential scanning calorimetry)

Example 2: Preparation of microsphere with poly-L-lactic acid-polyethylene glycol di-block copolymer (DiPLE)

Microsphere was prepared from poly-L-lactic acid(PLLA) and poly-L-lactic acid-polyethylene glycol di-block copolymer (DiPLE) by the oil-in-water (O/W) emulsion solvent evaporation method which is conventionally used in the hydrophobic drug manufacture.

In order to determine the optimum content of polymeric surfactant, DiPLE obtained in Example 1 within microsphere, the morphology of microsphere was observed according to the mixing ratios of DiPLE.

First, 250 mg of poly-L-lactic acid and DiPLE(0, 2, 4, 6, 8, 10, 20 and 30 wt%) were dissolved into 5 ㎖ of dichloromethane, and then subjected to homogenization at 24,000 rpm for 10 minutes with a homogenizer under vigorous stirring while injecting 40 ㎖ of aqueous 2 w/v% polyvinyl alcohol solution with a needle gauge thereinto. Dichloromethane was evaporated for 2 hours at 40℃. The microsphere formed by poly-L-lactic acid coagulation was washed three times with distilled water to remove polyvinyl alcohol, collected by centrifugation and then freeze-dried for 24 hours.

Example 3: Preparation of microsphere with poly-D,L-lactic acid-polyethylene glycol tri-block copolymer (TriPLE)

Microsphere was prepared by the oil-in-water (O/W) emulsion solvent evaporation method. 200 mg of poly-D,L-lactic acid and the synthesized TriPLE(0, 5, 10, 15, 20, and 100 wt%) were dissolved into 5 ㎖ of dichloromethane, and the organic solution was vigorously stirred(rpm 1,000)

with a mechanical stirrer while pouring it into 200 ㎖ of aqueous 2 w/v% polyvinyl alcohol solution. The subsequent procedures were followed by Example 2.

Example 4: Inclusion of retinoic acid

The work for incorporating retinoic acid into the microsphere was carried out in a dark room in order to prevent retinoic acid from decomposition by light.

4.1 Preparation of poly-L-lactic acid microsphere with DiPLE
Two types of microspheres were prepared having particle size of 1~10 ㎛ and 20~100 ㎛, respectively.

In order to prepare the microsphere having particle size of 1~10 ㎛, 250 mg of poly-L-lactic acid and DiPLE(0, 4, and 8 wt%) and retinoic acid (2, 4, and 8 wt%) were first dissolved into 5 ㎖ of dichloromethane, and then subjected to homogenization at 24,000 rpm for 10 minutes with a homogenizer under vigorous stirring while injecting 40 ㎖ of aqueous 2 w/v% polyvinyl alcohol solution with a needle gauge thereinto. The remaining procedures are the same as in Example 2.

In order to prepare the microsphere having particle size of 20~100 ㎛, 3.75g of poly-D,L-lactic acid, DiPLE (8w%) and retinoic acid (4 wt%) were dissolved into 75 ㎖ of dichloromethane, and the organic solution was vigorously stirred(rpm 1,000) with a mechanical stirrer while pouring it into 600 ㎖ of aqueous 2 w/v% polyvinyl alcohol solution. The remaining procedures are the same as in Example 2.

4.2: Preparation of poly-D,L-lactic acid microsphere with DiPLE

Microsphere was prepared by the oil-in-water (O/W) emulsion solvent evaporation method. First, 400 mg of poly-D,L-lactic acid (Molecular weight: 17,500), DiPLE(0 or 8 wt%) and retinoic acid (10 wt%) were dissolved into 10 ㎖ of dichloromethane, and the organic solution was stirred(rpm 1,000) with a mechanical stirrer while pouring it into 200 ㎖ of aqueous 2 w/v% polyvinyl alcohol solution. The remaining procedures are the same as in Example 2.

4.3: Preparation of microsphere with triPLE

Microsphere was prepared by the O/W emulsion solvent evaporation method. 600 mg of TriPLE and retinoic acid (0, 5, or 10 wt%) were dissolved into 15 ㎖ of dichloromethane, and the organic solution was stirred(rpm 1,000) with a mechanical stirrer while pouring it into 200 ㎖ of aqueous 2 w/v% polyvinyl alcohol solution. The remaining procedures are the same as in Example 2.

Experiment 1: Characterization of microsphere

The morphology of the microspheres obtained in Examples 2 and 3 was observed with scanning electron microscope(SEM). In order to investigate the dispersibility in the dispersed solution, the degree of dispersion of microspheres was evaluated in phosphate buffer solution of pH 7.4, and I(ionic strength) 0.15.

1.1. Poly-L-lactic acid microsphere with DiPLE

The morphology of microsphere according to the content of DiPLE is shown in Fig. 1 (a), (b), (c) and (d). As the content of DiPLE increases, the surface of microsphere became irregular. Microsphere having smooth surface was obtained at the content of up to 8wt% of DiPLE.

In the dispersibility test within PBS, the microsphere containing 2% or more of PLE was well dispersed, even without addition of the surfactant such as Tween 20 into the aqueous solution. Dispersibility was increased as the content of PLE increases.

The composition within the microsphere surface was analyzed by X-ray photoelectric spectrophotometry as shown in Fig. 2. The peaks at 285.5 eV, 287.5 eV and 289.6 eV correspond to the binding energy of -CH-, -CO- and -CO_2- of PLLA, respectively and the peak at 286.55 eV corresponds to C-C-O- of polyethylene glycol.

As can be seen from Fig. 2, the relative strength of the peak at 286.55 eV due to PEG chain was increased as the content of PLE within the microsphere increases. This suggests that as the content of DiPLE increases, the density of PEG chain on the microsphere surface increases. This is because dispersibility in PBS solution increases as the content of PLE increase.

As a result of SEM observation and the dispersion experiment within PBS, it was confirmed that the suitable DiPLE content for preparing microsphere according to the invention is within the range of 2～8 wt%.

1.2. Poly-D,L-lactic acid microsphere with TriPLE

The prepared microspheres showed diverse surface morphology according to the kinds of TriPLE and the mixing ratios thereof as shown in Fig. 3 and the differences in size was not observed in the microspheres. Generally, as the mixing ratio of TriPLE increases, the surface of microsphere became a wrinkled shape and when the mixing ratio is 100 %, microspheres in irregular shape were obtained (Fig. 3 a~c)).

In addition, if the ratio of central polyethylene glycol blocks to the poly-L-lactic acid blocks in both ends increases, the surface wrinkles were increased (Fig. 3 (b) and (e)).

In the microspheres that the third group of TriPLE is mixed, smooth surface of microsphere was observed as in the microsphere prepared with poly-D,L-lactic acid only, even if the mixing ratio was up to 20 wt%.

Experiment 2: Analysis of microsphere based on particle size and content of retinoic acid

2.1. Poly-L-lactic acid microsphere with DiPLE

The morphology of microsphere according to the changes in the content of retinoic acid was observed with SEM and the results are shown in Fig. 4 (a)~(c). When the size of microsphere is 1~10 μm, microsphere maintained overall rounded shape as can be seen from Fig. 4(a) to the extent that the content of retinoic acid was up to 4 wt%. However, partially irregular shapes were observed in the microsphere containing 8 wt% of retinoic acid (See, Fig. 4(b)).

When the size is 20~100 μm, as can be seen from fig 4(c), microspheres

the surface of which is rough and bold-wrinkled lines were formed even if the content of retinoic acid is 4wt%.

2.2. Microsphere prepared with TriPLE

Fig. 4 (d)~(e) is a SEM photograph of microsphere prepared from TriPLE 2-1 and retinoic acid (5 and 10 wt%). When prepared from TriPLE only, round, but irregular shaped microsphere was formed. If the drug is contained in the microsphere, this irregularity also increases, and thus, the increase in drug content changed the rounded shape into wrinkled shape.

2.3. Determination of retinoic acid content in microsphere

The inclusion ratio of retinoic acid into microsphere was determined by measuring ultraviolet(UV) absorbance at 365 nm and comparing the values with calibration curve after dissolving the drug containing microsphere into dichloromethane. The inclusion ratio of retinoic acid was not significantly changed according to the content of PLE or retinoic acid and the inclusion ratio was 90% or more in all cases.

Experiment 3: Release experiment of retinoic acid

Drug release experiment was conducted for the poly-L-lactic acid microsphere in which DiPLE and retinoic acid are mixed as follows:

First, after 10 mg of microsphere containing retinoic acid and 0.5 ㎖ of PBS were added into 1.5 ㎖ microtube, the solution was completely dispersed. The dispersed solution was then put into 6×1.6cm cellulose acetate membrane and each end of the membrane was sealed. Then, the

membrane was immersed in water bath containing 36 ℓ of PBS and stirred at 20 rpm. PBS within the water bath was exchanged at days 9 and 30.

At each measuring period, residual amount of retinoic acid within the microsphere was measured with UV light after membrane was taken from the water bath, washed, dried, and dissolved into dichloromethane. The overall procedures were conducted in a dark room considering the nature of retinoic acid which is sensitive to light.

The results on drug release test for the poly-L-lactic acid microsphere prepared by changing the contents of DiPLE and retinoic acid are shown in Fig. 5 (a)(b)(c). As can be seen from Fig. 5 (a)(b)(c), it was confirmed that retinoic acid in the microsphere according to the invention was released over 35 days and the release rate of retinoic acid from the microsphere was controlled according to the contents of DiPLE and retinoic acid. Especially, in the microsphere containing each 4wt% of DiPLE and retinoic acid, the drug release curve showed the release pattern similar to zero order drug release which reveals a nearly constant mode in drug release rate.

Experiment 4: Animal test

In order to investigate the inhibitory effect against tumour growth by administration of the microsphere containing retinoic acid into mice, 2×10^6 cell/㎖ of tumour cells taken from the patients having head and neck cancer and incubated were subcutaneously injected into the both back sides of the experimental mice weighing 15～31g at the age of 1.5～2 months in 0.5 ㎖ unit. Then, the mice were divided into two groups. The first group was administered with the microsphere which does not contain

retinoic acid, and the second group was administered with poly-L-lactic acid microsphere containing retinoic acid(DiPLE 8 wt%/ RA 4 wt%) in each 100 mg/kg dose, and then the size of tumour was recorded at each one week interval. In the meantime, the microsphere was sterilized with ethylene oxide gas before intraperitoneal injection. Tumour cells and microspheres were injected into mice and the changes in tumour growth after 5 weeks were represented in Fig. 6 (a) and (b). Tumour cells were grown up to the average size of 1700 mm^3 in the mice inoculated with microsphere without retinoic acid (See, 6(a)). However, tumour cells were grown to 300 mm^3 in the mice inoculated with microsphere with retinoic acid (See, 6(b)). This value corresponds to 18% of the control, which suggests that the microsphere containing retinoic acid according to the present invention remarkably and effectively inhibits the tumour cell growth.

Industrial Applicability

Since cytochrome P450 which metabolizes retinoic acid is induced even by a small amount of retinoic acid, repetitive administration of retinoic acid induces a problem that retinoic acid is rapidly decomposed into polar metabolite and thus, effective blood level cannot be maintained. This problem can be solved by a controlled drug release system for retinoic acid according to the present invention which slowly and continuously release retinoic acid over 5 weeks. Especially, in the microsphere containing each 4wt% of DiPLE and retinoic acid, the drug release curve showed the release pattern similar to zero order drug release which reveals a nearly constant mode in drug release rate. This novel drug release system can minimize resistance induction by the oral retinoic acid administration, and possible to control the dissolution of microsphere and

release rate of retinoic acid. Therefore, this system can effectively be used in the prevention or treatment of leukemia and various other cancers.

Claims

1. A controlled drug release system for retinoic acid which comprises microsphere in which biodegradable polymer and amphoteric block copolymer are mixed and retinoic acid incorporated into the microsphere.

2. The drug release system for retinoic acid according to Claim 1, wherein the retinoic acid is selected from the group consisting of all-trans-retinoic acid, 13-cis-retinoic acid, 9-cis-retinoic acid, other retinoids and the mixture thereof.

3. The drug release system for retinoic acid according to Claim 1, wherein the biodegradable polymer is selected from the group consisting of natural polymer, synthetic polymer and the mixture thereof.

4. The drug release system for retinoic acid according to Claim 1, wherein the amphoteric block copolymer is di-, tri- or multi-block copolymer or graft copolymer of the biodegradable polymer according to claim 3 and polyethylene glycol.

5. The drug release system for retinoic acid according to Claim 1 or 5, wherein the mixing ratio of the biodegradable polymer and the amphoteric block copolymer is 1:0~100 part by weight.

6. The drug release system for retinoic acid according to Claim 1, wherein the mixing ratio of retinoic acid and microsphere is between 0.1 ~ 50 wt% based on the weight of microsphere.

7. The drug release system for retinoic acid according to Claim 1, wherein

the particle size of the microsphere is between 0.001 and 1000 μm.

8. The drug release system for retinoic acid according to Claim 1 or 5, wherein the amphoteric block copolymer comprises 2 ~ 8 wt% of DiPLE or up to 20 wt%of TriPLE based on the total weight of the release system.

9. The drug release system for retinoic acid according to any of Claims 1 to 8 for use in the prevention or treatment of patients suffering from the diseases selected from the group consisting of acute promyelocytic leukemia, head and neck cancer, skin cancer, lung cancer, breast cancer, cervical cancer, bladder cancer, and acute promyelocytic leukemia.

10. A method of treating patients in need of retinoic acid administration, said method comprising the oral administration of the drug release system according to any of Claims 1 to 9 into the patients.

Fig.1a

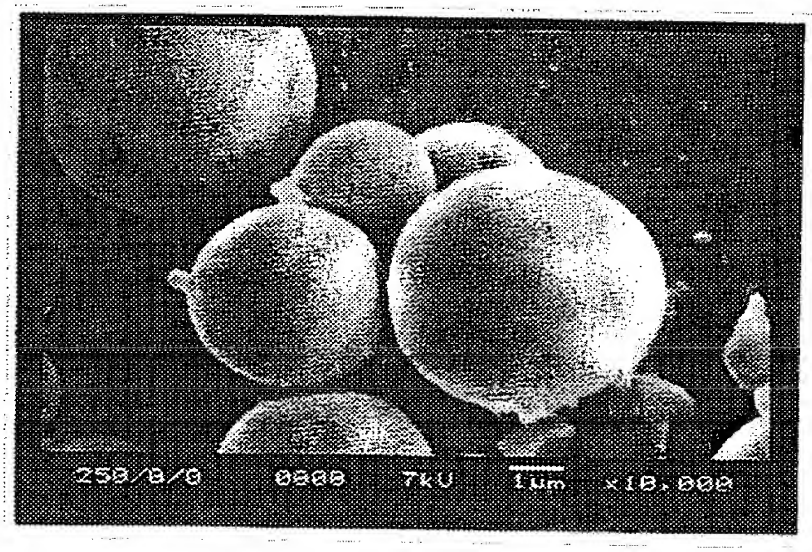


Fig.1b

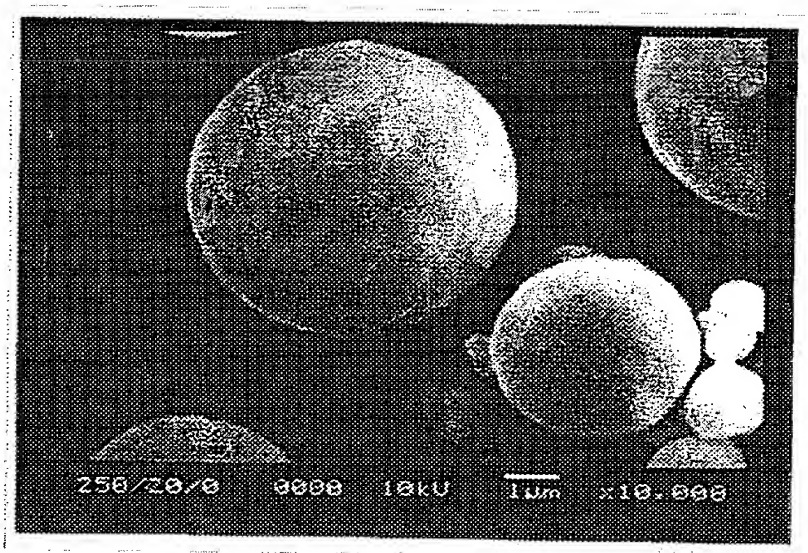


Fig.1c

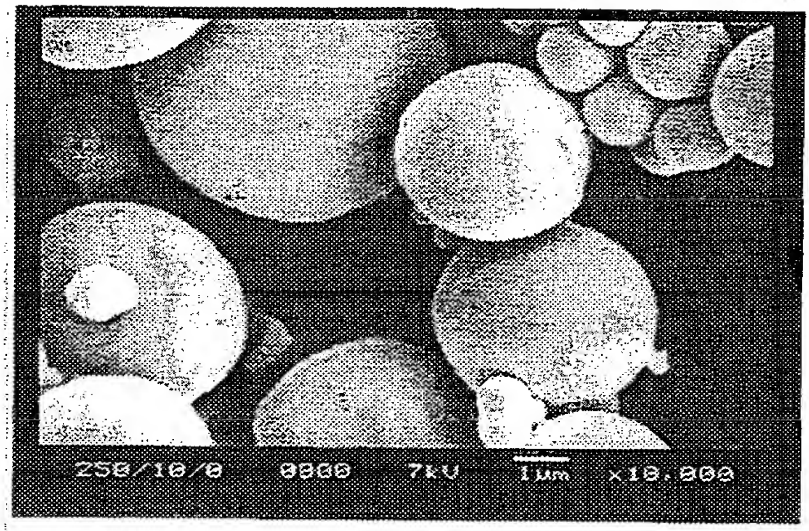


Fig.1d

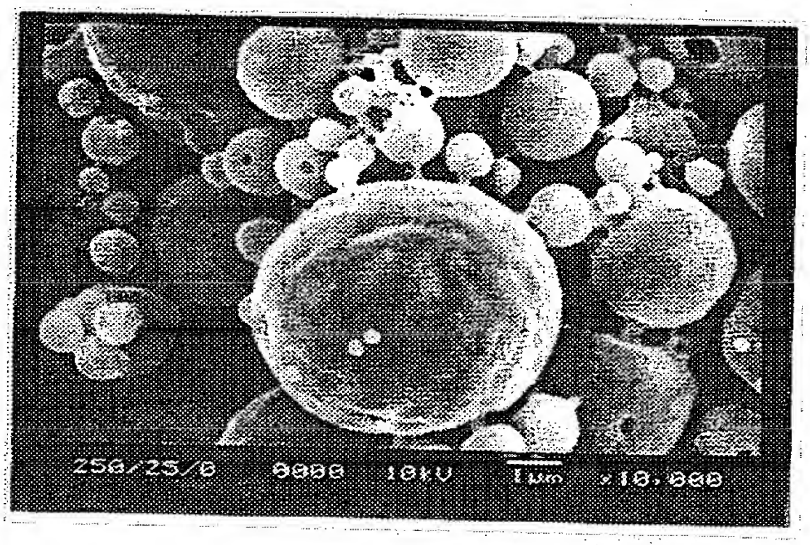


Fig.2a

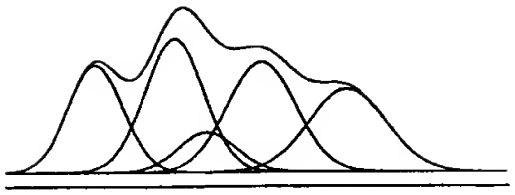


Fig.2b

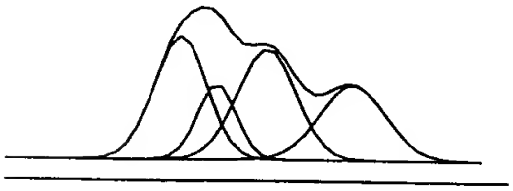


Fig.2c

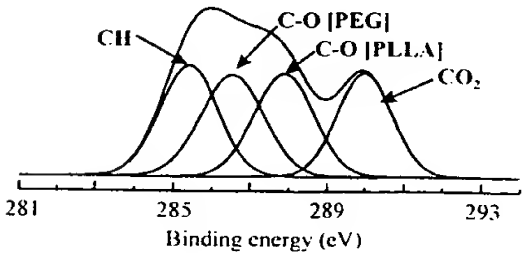


Fig.3a

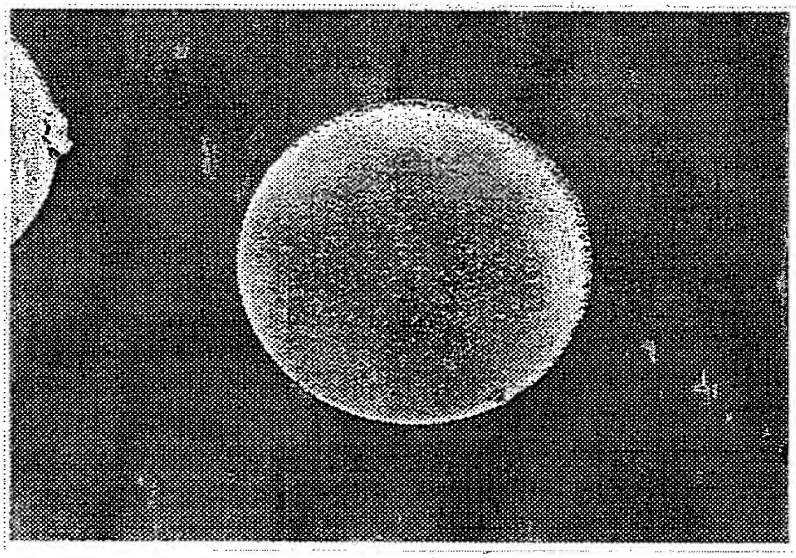


Fig.3b

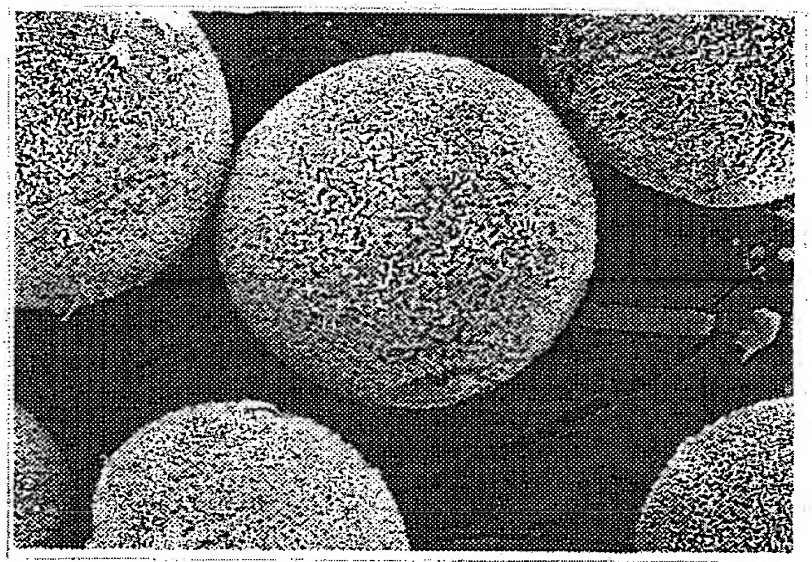


Fig.3c

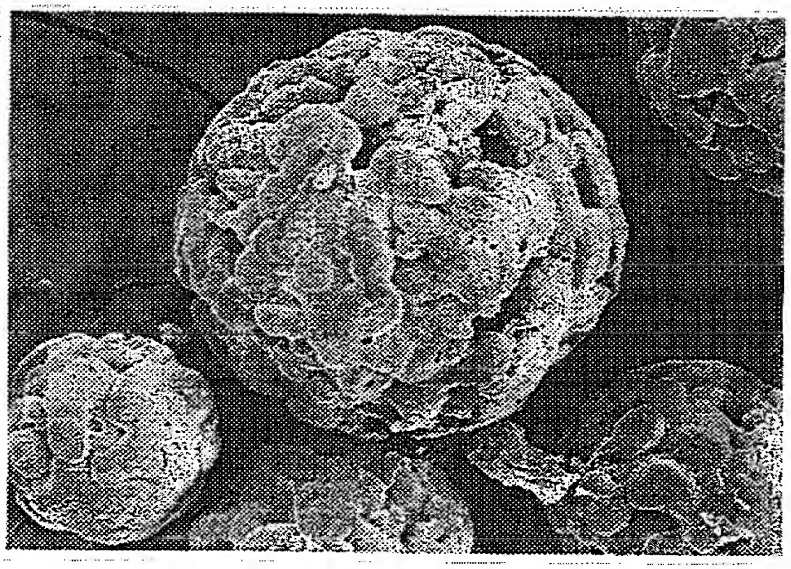


Fig.3d

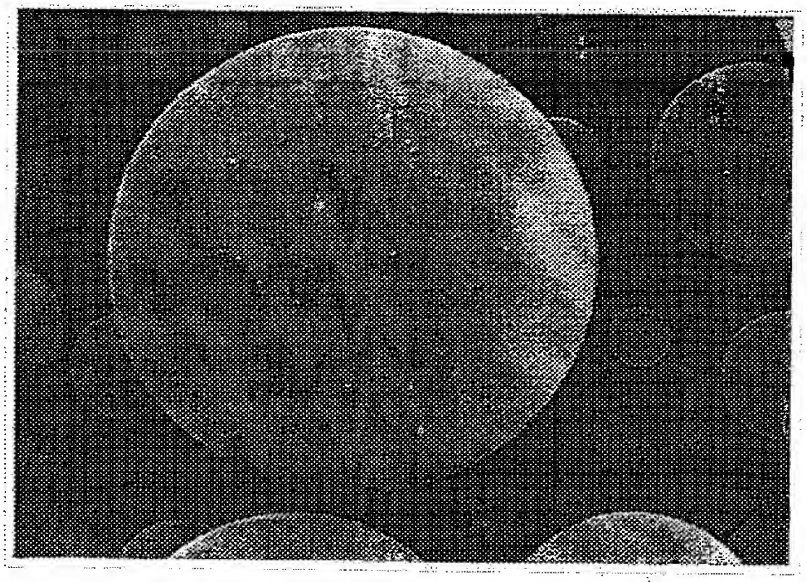


Fig.3e

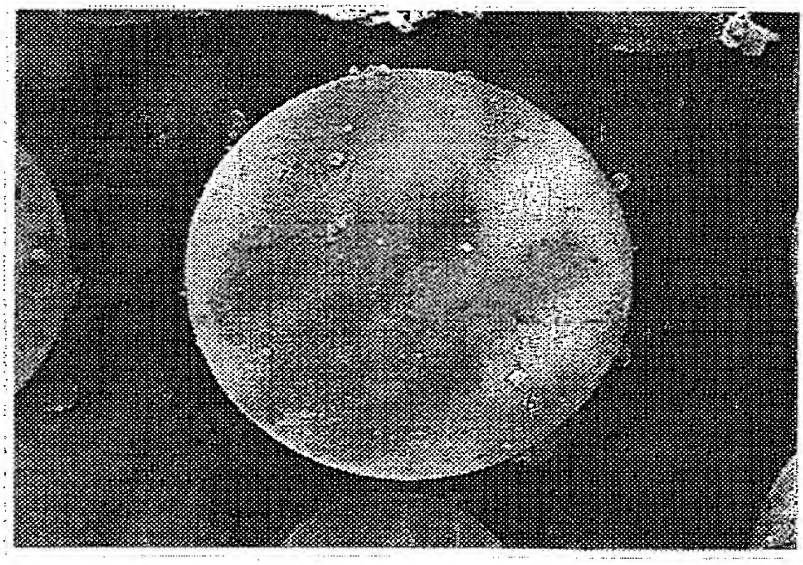


Fig.3f

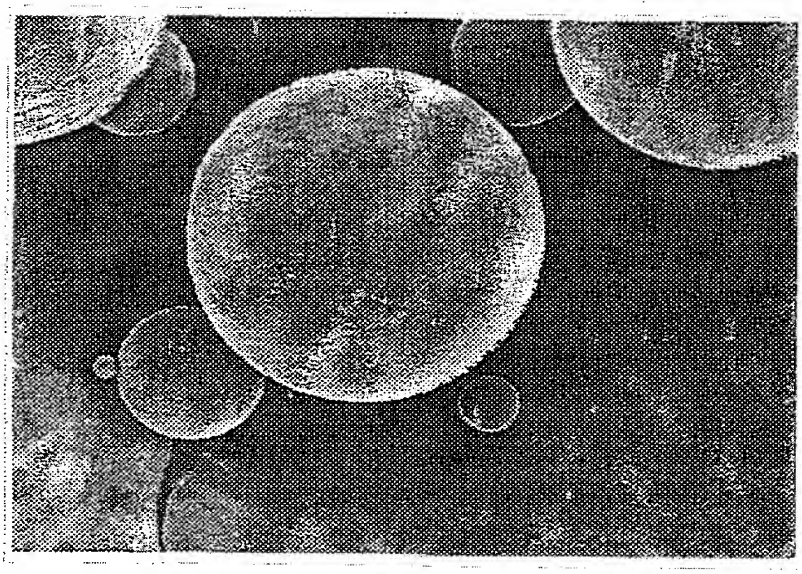


Fig.4a

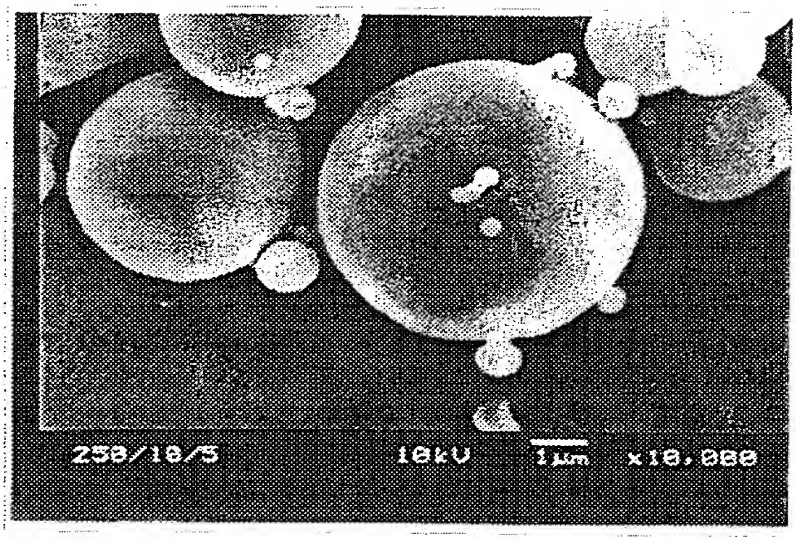


Fig.4b

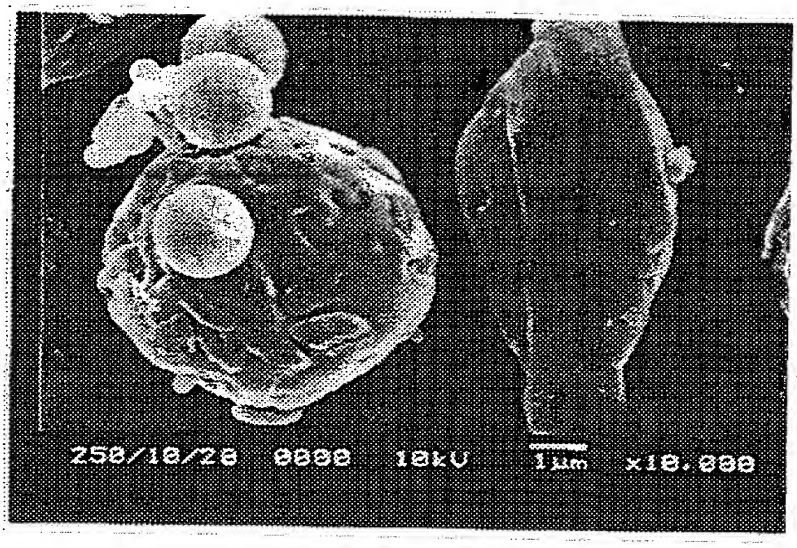


Fig.4c

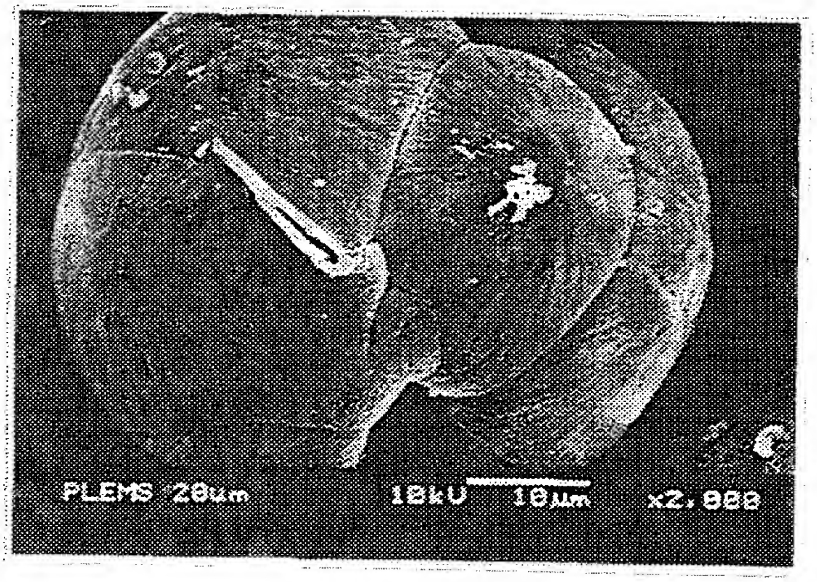


Fig.4d

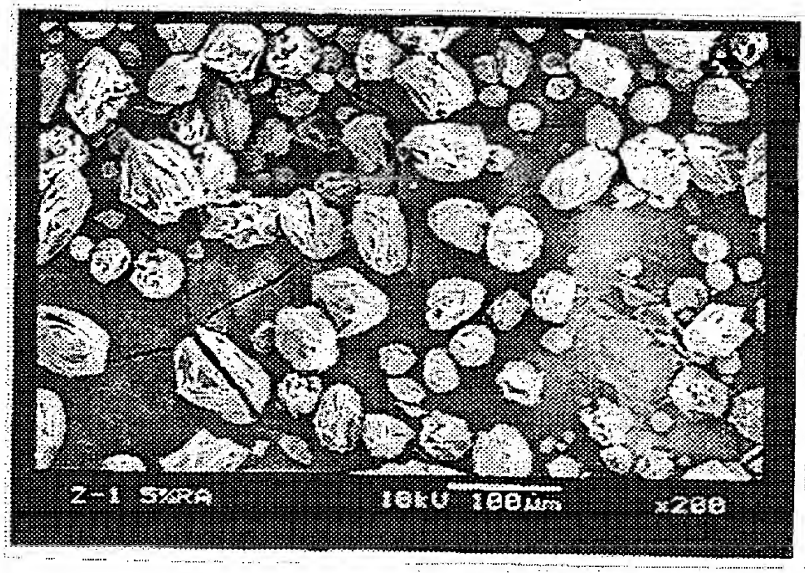


Fig.4e

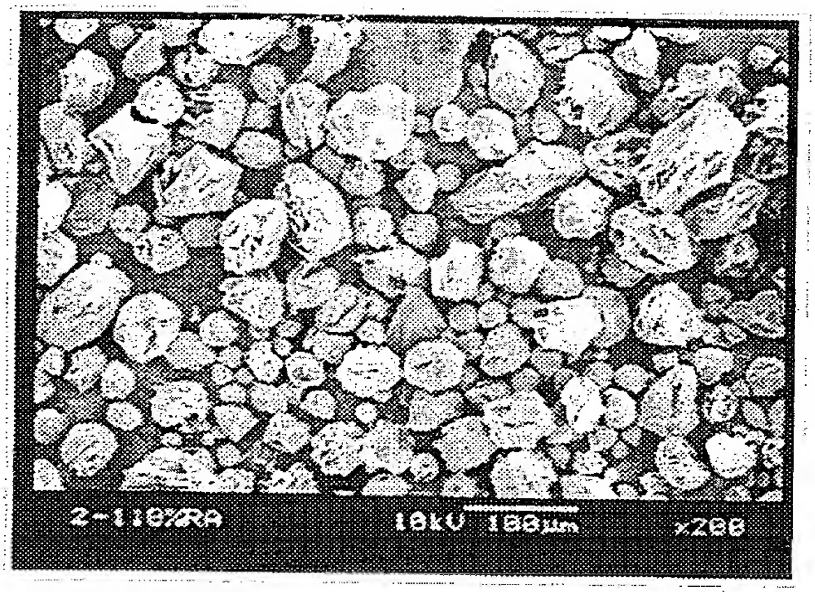


Fig.5a

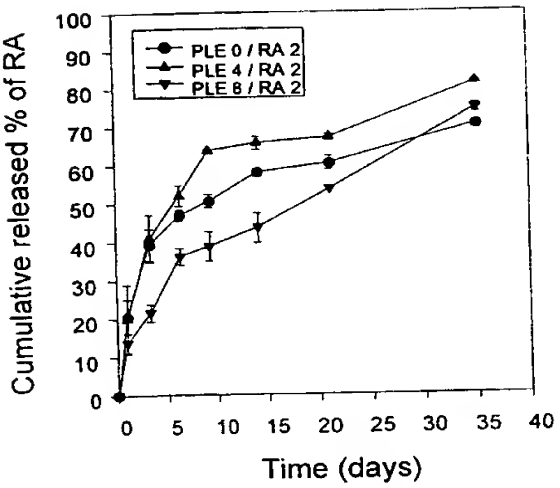


Fig.5b

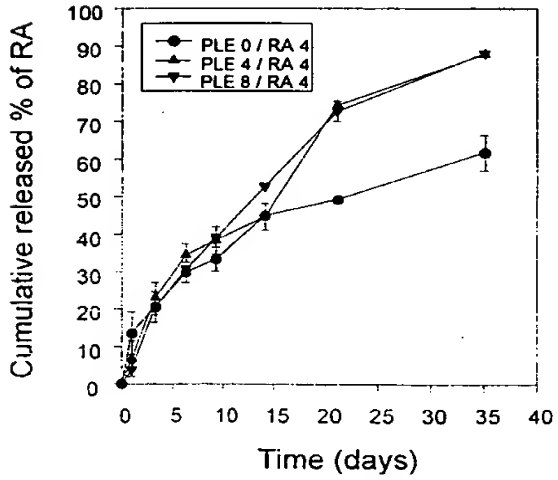


Fig.5c

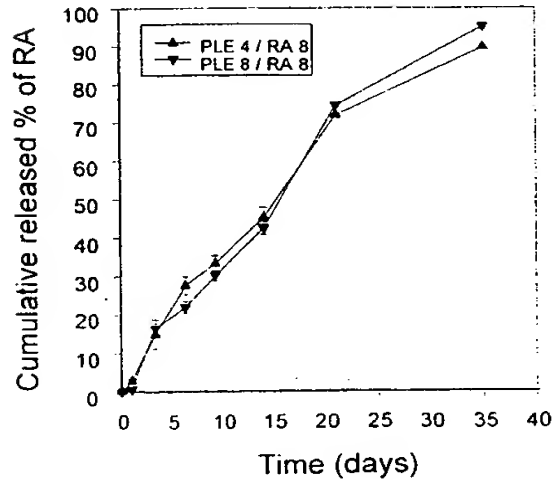


Fig.6a

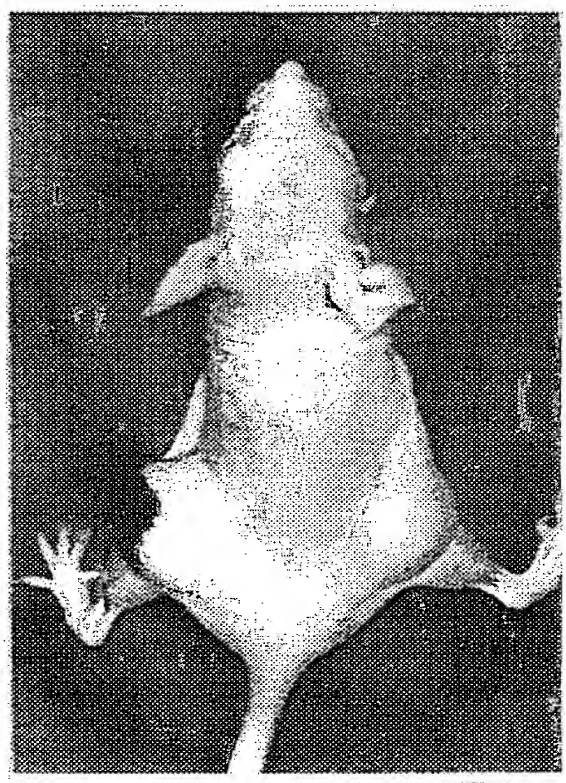
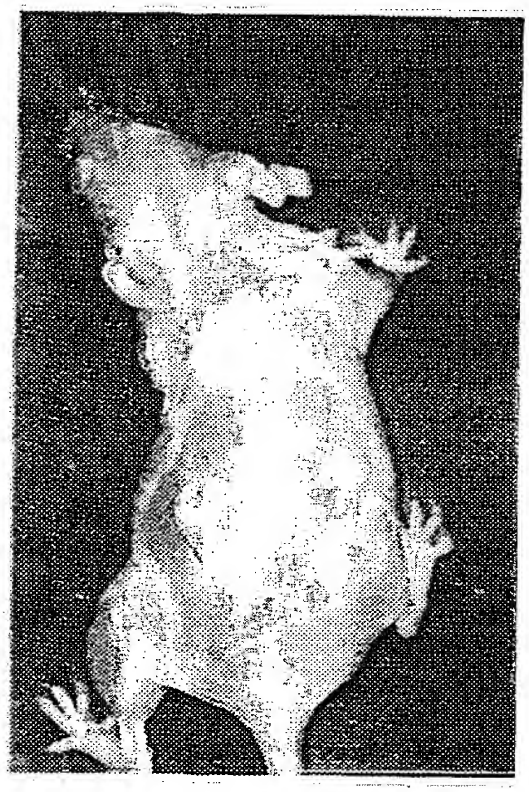


Fig.6b



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00589

A. CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A 61 K 31/203; A 61 K 9/10; A 61 K 9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, PAJ, medline, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/15287 A1 (MACROMED INC.), 01 May 1997 (01.05.97), abstract; page 16, line 18-21; page 16, line 18 - page 17, line 3; page 17, lines 35-37; claims 1-12,15.	1,3-8
Y	WO 96/28143 A1 (BOEHRINGER MANNHEIM GMBH), 19 September 1996 (19.09.96), abstract; page 7, lines 30-34; page 8, lines 14-20; page 10, lines 1-3.	1,3-8
Y	US 5534261 A (RODGERS et al.), 09 July 1996 (09.07.96), abstract.	1-8
Y	GIORDANO et al. "Sustained delivery of retinoic acid from microspheres of biodegradable polymer in PVR", abstract, Invest Ophthalmol Vis Sci, August 1993; 34(9) [online][retrieved on 1999-12-29] Retrieved from Database Medline on Dialog, US National Library of Medicine, (Bethesda, MD, USA), No.93346177.	1-3

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 January 2000 (04.01.00)	16 February 2000 (16.02.00)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/200	Authorized officer Krenn Telephone No. 1/53424/435

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00589

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a therapeutic method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound composition (see PCT-Article 17, rule 39.1.iv).

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 99/00589

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
WO	A1	9715287	01-05-1997	AU	A1	75200/96	15-05-1997
				EP	A1	863745	16-09-1998
				EP	A4	863745	22-12-1999
				JP	T2	11513985	30-11-1999
				US	A	5702717	30-12-1997
WO	A1	9628143	19-09-1996	AU	A1	50041/96	02-10-1996
				CA	AA	2214889	19-09-1996
				DE	A1	19542837	22-05-1997
				EP	A1	814778	07-01-1998
				JP	T2	11501642	09-02-1999
				DE	A1	19513659	12-09-1996
US	A	5534261	09-07-1996			none	

PCT REQUEST

PC99026-SP

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0 0-1	**For receiving Office use only** International Application No.	
0-2	International Filing Date	Rec'd PCT/PTO 28 MAR 2001
0-3	Name of receiving Office and "PCT International Application"	
0-4 0-4-1	**Form - PCT/RO/101 PCT Request** Prepared using	PCT-EASY Version 2.84 (updated 01.07.1999)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Korean Industrial Property Office (RO/KR)
0-7	**Applicant's or agent's file reference**	PC99026-SP
I	**Title of invention**	CONTROLLED DRUG RELEASE SYSTEM OF RETINOIC ACID
II II-1 II-2 II-4 II-5 II-6 II-7 II-8 II-9	**Applicant** This person is: Applicant for Name Address: State of nationality State of residence Telephone No. Facsimile No.	 applicant only all designated States except US KWANGJU INSTITUTE OF SCIENCE AND TECHNOLOGY 572, Ssangam-dong, Kwangsan-ku, 506-712 Kwangju Republic of Korea KR KR (82-62) 970-2302 (82-62) 970-2304
III-1 III-1-1 III-1-2 III-1-4 III-1-5 III-1-6 III-1-7	**Applicant and/or inventor** This person is: Applicant for Name Address: State of nationality State of residence	 applicant only all designated States except US SHIN POONG PHARMACEUTICAL CO., LTD. 434-4, Moknae-dong, Ansan-shi, 425-100 Kyunggi-do Republic of Korea KR KR

PCT REQUEST PC99026-SP

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III-2	**Applicant and/or inventor**	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	BYUN, Young-Ro
III-2-5	Address:	Keumkwang Apt. 103-1305, Wallgae-dong, Kwangsan-ku, 506-302 Kwangju Republic of Korea
III-2-6	State of nationality	KR
III-2-7	State of residence	KR
III-3	**Applicant and/or inventor**	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	KIM, Sang-Yoon
III-3-5	Address:	Woosung Apt. 3-707, Daechi 3-dong, Kangnam-ku, 135-283 Seoul Republic of Korea
III-3-6	State of nationality	KR
III-3-7	State of residence	KR
III-4	**Applicant and/or inventor**	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	KIM, Sun-Hee
III-4-5	Address:	Woosung Apt. 3-707, Daechi 3-dong, Kangnam-ku, 135-283 Seoul Republic of Korea
III-4-6	State of nationality	KR
III-4-7	State of residence	KR
III-5	**Applicant and/or inventor**	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	CHOI, Yong-Doo
III-5-5	Address:	Jeungheung Park 2-1508, Nongsung 1-dong, Seo-ku, 502-201 Kwangju Republic of Korea
III-5-6	State of nationality	KR
III-5-7	State of residence	KR

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III-6	**Applicant and/or inventor**	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	HAN, In-Suk
III-6-5	Address:	G 105-1025, East Olympic Lease Core, Salt Lake-city, UT 84117 United States of America
III-6-6	State of nationality	KR
III-6-7	State of residence	US
III-7	**Applicant and/or inventor**	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	LEE, Kwang-Sun
III-7-5	Address:	Kwangjang Apt. 3-605, Yoido-dong, Yongdungpo-ku, 150-010 Seoul Republic of Korea
III-7-6	State of nationality	KR
III-7-7	State of residence	KR
III-8	**Applicant and/or inventor**	
III-8-1	This person is:	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	KIM, Chul-Hee
III-8-5	Address:	Chungku Apt. 210-1050, Yangjimaeul, Soonae-dong, Bundang-ku, 463-020 Sungnam-shi Republic of Korea
III-8-6	State of nationality	KR
III-8-7	State of residence	KR
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	CHOI, Kyu-Pal
IV-1-2	Address:	824-20, Yeoksam-dong, Kangnam-ku, 135-080 Seoul Republic of Korea
IV-1-3	Telephone No.	(82-2) 555-6888
IV-1-4	Facsimile No.	(82-2) 555-9888
IV-1-5	e-mail	HANSUNGP@chollian.net

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V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW SD SL SZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AL AM AT AU AZ BA BB BG BR BY CA CH&LI CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	**Exclusion(s) from precautionary designations**	NONE
VI-1	**Priority claim of earlier national application**	
VI-1-1	Filing date	01 October 1998 (01.10.1998)
VI-1-2	Number	1998-41426
VI-1-3	Country	KR
VII-1	**International Searching Authority Chosen**	Austrian Patent Office (ISA/AT)

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VIII	Check list	number of sheets	electronic file(s) attached
VIII-1	Request	5	-
VIII-2	Description	19	-
VIII-3	Claims	2	-
VIII-4	Abstract	1	kwangju.txt
VIII-5	Drawings	11	-
VIII-7	TOTAL	38	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-9	Separate signed power of attorney	✓	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	**Figure of the drawings which should accompany the abstract**	1	
VIII-19	**Language of filing of the international application**	English	
IX-1	**Signature of applicant or agent**		
IX-1-1	Name (LAST, First)	CHOI, Kyu-Pal	

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/AT
10-6	**Transmittal of search copy delayed until search fee is paid**	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

PCT (ANNEX - FEE CALCULATION SHEET)

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(This sheet is not part of and does not count as a sheet of the international application)

0 0-1	**For receiving Office use only** International Application No.	
0-2	Date stamp of the receiving Office	

0-4 0-4-1	**Form - PCT/RO/101 (Annex)** **PCT Fee Calculation Sheet** Prepared using		PCT-EASY Version 2.84 (updated 01.07.1999)		
0-9	**Applicant's or agent's file reference**		PC99026-SP		
2	**Applicant**		KWANGJU INSTITUTE OF SCIENCE AND TECHNOLOGY, et al.		
12	**Calculation of prescribed fees**		fee amount/multiplier	total amounts (KRW)	
12-1	Transmittal fee	T	⇨	45,000	
12-2	Search fee	S	⇨	214,500	
12-3	International fee Basic fee (first 30 sheets)	b1	544,600		
12-4	Remaining sheets		8		
12-5	Additional amount	(X)	12,600		
12-6	Total additional amount	b2	100,800		
12-7	b1 + b2 =	B	645,400		
12-8	Designation fees Number of designations contained in international application		82		
12-9	Number of designation fees payable (maximum 10)		10		
12-10	Amount of designation fee	(X)	125,700		
12-11	Total designation fees	D	1,257,000		
12-12	PCT-EASY fee reduction	R	-167,600		
12-13	Total International fee (B+D-R)	I	⇨	1,734,800	
12-17	**TOTAL FEES PAYABLE (T+S+I+P)**		⇨	1,994,300	
12-19	**Mode of payment**		cash		

VALIDATION LOG AND REMARKS

13-2-6	**Validation messages** **Contents**	Green? Priority 1. The priority document is not enclosed. (The applicant must furnish it within 16 months from the earliest priority date claimed)
13-2-10	**Validation messages** **For receiving Office/International Bureau use only**	Green? Verify electronic data for consistency against printed form.

PCT

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PCT-EASY INFORMATION SHEET

(For applicant use only, DO NOT submit this sheet with the international application)

VALIDATION LOG

	Contents
Green?	Priority 1. The priority document is not enclosed. (The applicant must furnish it within 16 months from the earliest priority date claimed)
	For receiving Office/International Bureau use only
Green?	Verify electronic data for consistency against printed form.

Before submitting the International Application, please carefully verify that:

-the information contained on printed Request form is correct;
-Box IX of the Request form has been signed;
-all elements of the international application as indicated in Box VIII of the Request form have been attached; and,
-the diskette containing the PCT-EASY zip file of the International Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.

ATTENTION

DO NOT modify any indications on the Request form printout. The attached PCT-EASY application has been locked. If an error or an omission is discovered at this time, you must copy the submitted application as a template and make the change or correction in a new application (using the submitted application as a template). You may create such a template by copying the submitted application from the "Stored Forms" folder to the "New PCT Forms" folder. Open the new (.0WO) file created in the "New PCT Forms" folder, correct the errors and proceed with the submission process again.

Claims

(Amended under PCT Article 34)

1. A controlled drug release system for retinoic acid characterized in that retinoic acid is incorporated into a microsphere prepared by mixing a biodegradable polymer and an amphoteric AB type di-block copolymer together, wherein the retinoic acid is selected from the group consisting of all-trans-retinoic acid, 13-cis-retinoic acid, 9-cis-retinoic acid, other retinoids and the mixture thereof.

2. The drug release system for retinoic acid according to Claim 1, wherein the biodegradable polymer is selected from the group consisting of natural polymer, synthetic polymer and the mixture thereof.

3. The drug release system for retinoic acid according to Claim 1, wherein the biodegradable polymer is selected from the group consisting of poly-L-lactic acid, poly-D,L-lactic acid, and poly(lactic-co-glycolic acid).

4. The drug release system for retinoic acid according to claim 1. wherein the amphoteric block copolymer is poly-L-lactic acid-polyethyleneglycol or poly(lactic-co-glycolic acid)-polyethyleneglycol.

5. The drug release system for retinoic acid according to Claim 1, wherein the mixing ratio of the biodegradable polymer and the amphoteric block copolymer is 1:0~100 part by weight.

6. The drug release system for retinoic acid according to Claim 1, wherein the mixing ratio of retinoic acid and microsphere is between 0.1 ~ 50 wt% based on the weight of microsphere.

7. The drug release system for retinoic acid according to Claim 1, wherein the particle size of the microsphere is between 0.001 and 1000 ㎛.

8. The drug release system for retinoic acid according to Claim 1, wherein the amphoteric block copolymer comprises 1 ~ 20 wt% of DiPLE based on the total weight of the release system.

9. The drug release system for retinoic acid according to any one of Claims 1 to 8 for use in the prevention or treatment of patients suffering from the diseases selected from the group consisting of acute promyelocytic leukemia, head and neck cancer, skin cancer, lung cancer, breast cancer, cervical cancer, bladder cancer, and acute promyelocytic leukemia.

10. A method of treating patients in need of retinoic acid administration, comprising the oral administration of the drug release system according to any one of Claims 1 to 9 into the patients.